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It is a commonplace for disorders, long regarded as the undisputed province of the dermatologist, to be revealed as no more than the cutaneous expression of systemic disease. Disseminated lupus erythematosus and sarcoidosis are familiar examples. The same fate has now befallen urticaria pigmentosa: enlargement of lymph-nodes, liver, and spleen, defects of coagulation, and skeletal changes have all been recorded in association with the characteristic eruption. The purpose of the present paper is to describe the case of a patient with urticaria pigmentosa accompanied by such systemic changes, to review relevant reports, and to discuss the nature of the disorder.

Case Report

A single woman (St.B.H.C.R. 328860), aged 67 years, was admitted to St. Bartholomew's Hospital on December 27, 1956, with a complaint of abdominal pain, lassitude, and swelling of the ankles. Twelve years previously a claret-coloured eruption had appeared on the skin of the chest, and had spread within 10 months to cover the body. It caused no discomfort apart from irritation when she became warm. Biopsy at that time had established the diagnosis of urticaria pigmentosa. For 10 years she had suffered from attacks of epigastric pain and flatulence three hours after meals, sometimes accompanied by diarrhoea. On her admission to another hospital three years previously, splenic and hepatic enlargement had been noted. In the past six months there had been increasing lethargy, weakness, abdominal discomfort, and swelling of the ankles. For 12 weeks she had been confined to her bed. She had had no other illness of significance in the past, and she came of healthy stock.

Physical examination showed her to be pale and thin. The weight was 7 st. 8 lb. (48 kg.); she had no fever, a pulse frequency of 80 per minute, and a blood-pressure of 170/100. The violet papules of urticaria pigmentosa were scattered diffusely over the surface of the body, with normal skin separating the lesions (Plate 29, Fig. 1); friction resulted in some urtication, but there was no dermatographia. The mucosae were healthy. There was slight oedema of the ankles. No superficial lymph-nodes were palpable, but the liver was enlarged to 6 cm. and the spleen to 4 cm. below the costal margin. Rectal examination and sigmoidoscopy were normal. The heart, lungs, and nervous system were

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healthy and, apart from valgus deformity of the ankles, there were no skeletal abnormalities.

Investigations

1. *Haematological.* The red cells were 3,500,000 per cu.mm.; haemoglobin 8·7 g. per 100 ml.; packed-cell volume 29 per cent.; mean corpuscular volume 83 cu. μ; and mean corpuscular haemoglobin concentration 30 per cent. Reticulocytes were 2·1 per cent.; white blood cells 4,800 per cu.mm. (neutrophils 59 per cent., eosinophils 6 per cent., basophils 0, lymphocytes 33 per cent., and monocytes 2 per cent.); and platelets 54,000 per cu.mm. No abnormal cells were seen in the films. This count is representative of many made during the patient's stay in hospital. No mast cells were found in the peripheral blood after subcutaneous injection of 1 ml. of 0·1 per cent. solution of adrenaline hydrochloride. The erythrocyte sedimentation rate (Westergren) was 40 mm. in the first hour. The bleeding time (Duke) was 2 minutes 30 seconds; the whole-blood clotting time (Lee and White) 6 minutes 45 seconds; and the one-stage prothrombin time (Quick) 15 seconds (control 14 seconds). The blood group was A, rhesus positive. The Wassermann reaction was negative. Bone-marrow puncture showed normoblastic hyperplasia, with 9·5 per cent. eosinophils; no mast cells were seen. The serum bilirubin was 0·4 mg. per 100 ml.; faecal urobilinogen excretion (daily mean for a three-day period) was 70 mg.

2. *Tests of hepatic function.* The serum protein was 6·4 g. (albumin 4·4 g., globulin 2·0 g.) per 100 ml.; the electrophoretic pattern was normal. Thymol turbidity was 4 units, and zinc sulphate turbidity 5 units; bromsulphthalein excretion showed less than 1 per cent. retained after 45 minutes. Serum alkaline phosphatase was 13·5 to 45 King–Armstrong units, and serum acid phosphatase 1·5 King–Armstrong units per 100 ml.

3. *Metabolic tests.* Plasma bicarbonate was 22·3 m-equiv., serum chloride 108·5 m-equiv., serum sodium 140 m-equiv., and serum potassium 4 m-equiv. per litre. Serum calcium was 7·2 mg. and serum inorganic phosphate 3·1 mg. per 100 ml. *Fat balance*: over a three-day period with a daily intake of 70 g. of fat, 90 per cent. was absorbed. On a normal diet the daily loss of calcium in the urine was 45 mg., and of inorganic phosphate 18·2 mg. *Calcium balance*: over three-day periods, with a daily intake of 500 mg. of calcium 150 mg. were absorbed, and with a daily intake of 980 mg. 275 mg. were absorbed. The relative losses in the urine and faeces were normal.

4. *Miscellaneous tests.* The urine was chemically and microscopically normal, and was sterile on culture. Pharmacological assay of histamine-like substances gave normal results. Chromatographic examination showed no 5-hydroxyindoleacetic acid, and normal concentrations of coproporphyrin and uroporphyrin. Renal function tests gave normal results. The blood urea was 21 mg. per 100 ml.

5. *Radiological examination.* (1) *Alimentary tract.* An opaque meal revealed a small hernia at the oesophageal hiatus, and changes consistent with oesophageal varices. The colon was normal. No gall-bladder shadow was seen on oral cholecystography. (2) *The urinary tract* was normal except for a double pelvis and ureter on the right side. (3) *The skeleton. Ribs*: there was a general increase in density, without accentuation of trabecular structure. *Spine*: there was a general increase in density of the dorsal and lumbar vertebrae; surrounding the lower dorsal vertebrae was a fusiform soft tissue shadow (Plate 29, Fig. 2). *Pelvis*: there were many areas of increased density, tending to coalesce and give the appearance of a generalized change. *Femora*: the medullary cavities were almost obliterated by the homogeneous increase in the density of their cancellous structure. The cortex was thickened, but there was so little

difference in density between it and the medulla that its sharp outline was lost. About their centres the shafts were increased in thickness from 2·5 cm. to 4 cm. Their extremities showed a mottled increase in density (Plate 30, Fig. 3). *The tibiae and humeri* showed thinning of the cortex, which had almost disappeared at the distal ends. The bones had a general 'ground-glass' appearance and density, but in the upper parts of the humeri the changes were more patchy (Plate 30, Fig. 4). In the *radii and ulnae* diffuse osteoporosis had resulted in some loss of trabecular detail. In both bones bands of increased density extended partly or completely across the bone, representing healing pseudo-fractures (Plate 30, Fig. 5).

6. *Histological studies.* (1) *Biopsy of skin.* There is a perivascular infiltration with mast cells in the superficial layers of the corium. (2) *Biopsy of bone. Specimen 1.* A section of marrow from the inner aspect of the cortex of the ulna shows infiltration by sheets of spindle-shaped cells lacking any specific arrangement. They are uniform in type, with elongated nuclei, many displaying a constriction or 'waist' in the centre. The nuclei stain lightly with haematoxylin, but have a sharp nuclear membrane. The cell boundaries are poorly defined, and the cytoplasm eosinophilic and, in many cases, granular. These granules display metachromasia with dyes such as toluidine blue, confirming the view that the cells are mast cells. Only a minority, however, have the characteristics of mature mast cells; forms can be seen transitional between these and the predominant, lightly granulated spindle-shaped cell (Plate 31, Figs. 6 and 7). Section of the cortical bone shows a well-defined layer of subperiosteal new bone running the full length of the biopsy specimen: it is lamellar in type, and its appearance suggests that it has been present for some time. The vascular spaces in the new bone, as well as the Haversian spaces in the original cortex, show perivascular collections of mast cells. Near the centre of the specimen there is an interruption in the continuity of the original cortex, which is filled up with younger bone of the same type as that seen beneath the periosteum; the appearances suggest repair of a fracture in this region. *Specimen 2.* A section of the iliac crest shows infiltration of the marrow spaces by mast cells of varying maturity, similar to those observed in the ulnar marrow. Small islands of the original marrow persist in which the cellular constituents appear normal, except for the presence of isolated mature mast cells. In several areas the mast-cell infiltration has given place to fibrosis of the marrow spaces; here mast cells in reduced numbers can be seen mingling with more elongated cells having the characteristics of fibroblasts (Plate 31, Fig. 8). A silver-impregnated preparation shows an increase of argyrophile fibres in association with the more cellular foci of mast-cell infiltration. The bone pattern itself is quite abnormal; the trabeculae are irregular in shape, and considerably thicker than in health. Although osteoclastic erosion can be seen in some fields, it is clear that bone sclerosis is dominant, and the thickened trabeculae can be seen to consist of small fragments of the original bone structure embedded on a matrix of non-cellular new bone, lamellar in type, but showing a more irregular arrangement of the lamellae than normal adult bone.

Progress

Anaemia was repaired by blood transfusion, and oral calcium gluconate restored the serum-calcium and serum-phosphate levels to normal. Neither polymyxin ointment applied to the skin nor oral calciferol had any effect on the urticaria pigmentosa, or on other manifestations of the disease. Intensive physiotherapy was rewarded by the patient becoming able to stand, and by the time of her discharge on 23.5.57 she was able to walk with the aid of a stick.

She was readmitted to hospital on 24.6.58 for reassessment. There was little change in her general condition. Bone pain had become severe. The haematological picture showed an increasing eosinophilia, now amounting to 34 per cent. of 5,000 leucocytes per cu.mm.; in the marrow, eosinophils formed 13 per cent. of the nucleated cells. The tests of hepatic function showed progressive impairment; there was 15 per cent. retention of bromsulphthalein after 50 minutes, and the electrophoretic pattern of the plasma proteins showed a decrease in alpha-2 and beta globulins, and an increase in gamma globulin; the total plasma-protein figure was little changed, being 6·2 g. per 100 ml. (albumin 4·0 g., globulin 2·2 g.). The alkaline phosphatase was 13 King–Armstrong units, the serum calcium 6·2 mg. per 100 ml., and inorganic phosphate 2·7 mg. per 100 ml. A fat-balance test on this occasion revealed only 55 per cent. absorption. Progression of the vertical striate markings at right angles to the shaft of the femur was apparent on radiological review; in addition, a fresh healing fracture of the mid-shaft of the right radius was demonstrated. Irradiation of the left thigh to a dose of 200 r. resulted in relief of bone pain.

Discussion

Historical. Urticaria pigmentosa was first described by Nettleship in 1869; eight years later Unna showed that the histological basis of the eruption was nodular infiltration of the dermis by mast cells (see Unna, 1896). As early as 1919 Jeanselme and Touraine reported a case in which the rash was accompanied by enlargement of the liver and spleen, and, although histological proof was not sought, from their description there can be little doubt of the diagnosis. It was not until 1933 that further observations on this association were published, and the suggestion was made that the disease might be a form of 'pseudoleukaemia' (Touraine, Solente, and Renault, 1933). Post-mortem studies by Ellis (1949) first established the systematized nature of the disorder. His subject, a child of one year, had had urticaria pigmentosa from birth, and enlargement of the liver and spleen had been noted before death. At autopsy mast-cell infiltration was found in the liver, spleen, bone-marrow, lymph-nodes, and thymus. Radiological signs of skeletal disease were observed by Sagher, Cohen, and Schorr in 1952, but not until 1956 did biopsy prove these appearances to be due to infiltration by mast cells (Stark, Van Buskirk, and Daly). In addition to generalized bone changes, which are discussed later, a localized form has been described in which calcified deposits are seen in the long bones, or circumscribed areas of rarefaction in the long bones or the skull (Clynan and Rein, 1952; Calnan, 1953; Grupper, 1954; Degos, 1955; Reilly, Shintani, and Goodman, 1955). It has not yet been proved that the localized type of disease is due to mast-cell infiltration.

The above reports have established the pathological basis of urticaria pigmentosa as a proliferation of mast cells. At first purely cutaneous varieties were recognized, but it slowly became appreciated that these eruptions were sometimes associated with mast-cell infiltrations in the bones and in lymphoid tissues such as the spleen, liver, and lymph-nodes (Degos, Lortat-Jacob, Hewitt, and Ossipowski, 1952; Konrad and Winkler, 1953; Degos, Delort, and Ossipowski, 1953; Degos, Delort, and Hewitt, 1954). It is with this systematized form of

mast-cell proliferation that the present paper is concerned. It is true that other associations have been recorded. There is report of a patient showing urticaria pigmentosa and myelofibrosis (Rukavina, Dickinson, and Curtis, 1957) and another of what appeared to be a true tissue mast-cell leukaemia (Efrati, Klagman, and Spitz, 1957; Friedman, Will, Freiman, and Branstein, 1958). Splenic 'mastocytosis' without urticaria pigmentosa has recently been described (Ende and Cherniss, 1958). It is uncertain how these conditions are related to the syndrome under discussion, and they have therefore been excluded from consideration.

Incidence. Urticaria pigmentosa is a rare disease; one patient with this disorder is seen in every 2,500 new attendances at the Dermatological Department at St. Bartholomew's Hospital. In nearly three-quarters of cases the eruption appears during the first year of life (Ormsby and Montgomery, 1948). It remains uncertain how frequently the disease is limited to the skin and how frequently it is systematized. The recognition of systemic changes has been so recent that in series collected more than 10 years ago the possibility of such an event was not considered (Finnerud, 1923; Hannay, 1925). The incidence of associated skeletal change is variously recorded as one in seven (von Deutsch, Ellegast, and Nasko, 1956) and two in eight (Calnan, 1953). In both these series the changes were of the localized variety; in 52 cases collected by Sagher, radiological signs of localized bony disease were found in 17, and evidence of generalized change in two (Sagher and Schorr, 1956).

In addition to that reported here, there are 19 published instances in which the disease was undeniably systematized. These are recorded in detail in the Table. We have not included examples in which the only evidence for systematization was the presence of localized bone changes or lymph-node enlargement, without histological examination or a haemorrhagic state. In all the patients recorded in the Table the nature of the cutaneous eruption had been established by biopsy. Enlargement of the lymph-nodes was noted in six cases, of the liver in 13, and of the spleen in 12. Only scanty data of hepatic function are available; the prothrombin time was, however, abnormal in seven of the eight cases in which it was estimated.

Bone changes. Generalized bone changes were present in seven cases, and followed the pattern described by Sagher and Schorr (1956). In another three patients there were changes of a different type. In Case 8 there were multiple circumscribed areas of osteosclerosis in the pelvis, and reduction of the marrow space in the long bones to one-third of normal, with thickening of cortices; aspiration of the bone-marrow had revealed infiltration with mast cells and eosinophils. In Case 9 the epiphyseal centres of the left capitulum humeri, both olecrana, and the left trochlea, showed fragmentation. In Case 19 there was thickening of the frontal bone, increase in density of the diploic space, and irregular widening and loss of normal contour of the small and large tubular bones. The metacarpals were irregular in shape and size, with a tendency to rectangular configuration, coarsening of trabeculation, and thinning of the cortices; the middle phalanx of both the fifth fingers was shortened.

Systemic Involvement in Urticaria Pigmentosa

Case number	*Age*	*Sex*	*History*	*Lymphad-enopathy*	*Involvement of*		*Blood changes*	*Bone changes*	*Other features*	*Reference*
					Liver	*Spleen*				
1	5	M	4½ years	None	++	+++	Bleeding tendency. Mast cells in peripheral blood and bone-marrow	None	Lymph-node biopsy shows mast cells	Brodeur and Gardner (1956)
2	50	M	5 years	++	++	+++	Haemorrhagic tendency. Haemoglobin 75%. White cells 4,000/cu.mm.; normal differential count. Platelets 190,000/cu.mm. Bleeding time 13 min. Clotting time 20 min. Prothrombin time 50%. Protamine-tolerance test showed diminished coagulability. Marrow: numerous mast cells (6%)	None	Multiple infiltrative nodules. Splenic biopsy showed 70% mast cells. 47% mast cells in peripheral blood after splenic puncture; 15% after adrenaline. Biopsy of lymph-node showed reticular basophilia and no mast cells	Hissard, Moncourier, and Jacquet (1950, 1951 *a*, *b*) Degos, Lortat-Jacob, Mallarmé, and Sauvan (1951)
3	56	M	5 years	+	++	+++	White cells 14,000, after adrenaline 28,000/cu. mm.; no basophils. Platelets 120,000/cu. mm.	None	Liver biopsy: portal spaces infiltrated with lymphocytes, but no mast cells seen	Degos, Lortat-Jacob, Hewitt, and Ossipowski (1952)
4	1	F	1 year	None	+	+	White cells 16,700/cu. mm.; neutrophils 45%; band cells 8%; metamyelocytes 4%, but patient had gastroenteritis. Marrow aspirations normal	None	Autopsy showed mast-cell infiltration of bone-marrow and many viscera; liver showed periportal cirrhosis and mast-cell infiltration	Ellis (1949)
5	71	M	1 year	None	++	++	Haemoglobin 50%. White cells 3,600/cu. mm.; neutrophils 62%; lymphocytes 34%. Platelets 114,000 decreasing to 50,000/cu. mm. Marrow: 35% mast cells	None	Mucous membranes involved. Liver and spleen biopsy normal, but autopsy showed infiltration of liver and spleen with mast cells	Berlin (1955)
6	55	M	55 years	None	None	+	White cells 8,000/cu. mm.; neutrophils 61%; lymphocytes 29%; monocytes 4·5%; eosinophils 2·5%; basophils 2%; myelocytes 1%. Some lymphocytes were very large	None	Treated by irradiation of spleen	Touraine, Solente, and Renault (1933)
7	3 mths.	F	3 mths.	+	+	None	Haemoglobin 60%. White cells 6,500/cu. mm.; neutrophils 41%; monocytes 22%; lymphocytes 37%; no eosinophils. Marrow cellular but normal	None	Skin between rash infiltrated, but no nodules. Lymph-node biopsy showed intense lymphocytic proliferation	Degos, Delort, Hewitt, and Civatte (1954)
8	50	M	15 years	None	None	None	Haemoglobin and white cells normal. Platelets 68,000–105,000/cu. mm. Coagulation defect with increased heparin substance in blood. Prothrombin time 55%. Marrow: increase in eosinophils and many mast cells	Multiple. Circumscribed areas of osteosclerosis in pelvis. Reduction of marrow space in long bones to ½ normal; cortex thickened	..	von Deutsch, Ellegast, and Nasko (1956)
9	13	M	Presumed recent	None	None	None	Normal	Multiple. Fragmentation of several epiphyses	Localized urticaria pigmentosa (4 papules) but positive skin biopsy	Asboe-Hansen (1953)
10	53	M	4 years	None	++	None	Normal	Generalized	No appreciable change in condition over 5 years	Sagher, Cohen, and Schorr (1952)
11	55	F	5 years	None	None	None	Haemoglobin 80%. White cells 6,000/cu. mm.; neutrophils 27%; lymphocytes 54%; monocytes 17%; eosinophils 2%	Generalized	2 years later developed monocytic leukaemia with skin infiltrations, hepatospenomegaly, etc.	Sagher, Liban, Ungar, and Schorr (1956)

Case number	Age	Sex	History	Lymphadenopathy	Involvement of		Blood changes	Bone changes	Other features	Reference
					Liver	Spleen				
12	30	M	18 years	None	None	++	Normal blood and marrow	Generalized	Rectum mottled. Gastrointestinal upset with parallel activity of skin eruption	Bluefarb and Salk (1954)
13	34	M	Many years	None	++	+	Haemoglobin 82%. White cells 3,400/cu. mm.; normal differential count. Platelets 94,000/cu. mm. Marrow: aggregates of mast cells; lymphocytes increased	Generalized	Liver biopsy showed many mast cells, with periportal fibrosis. Localized bone changes also present (bone infarcts in pelvis and humerus)	Reilly, Shintani, and Goodman (1955)
14	54	M	30 years	None	None	None	Normal blood and marrow	Generalized	Bone biopsy showed mast-cell granulomata in narrow	Stark, Van Buskirk, and Daly (1956)
15	58	F	6 years	None	+++	+	Normal blood and marrow	Generalized	Liver biopsy normal. Bone biopsy showed infiltrate of non-granular mononuclear cells. Normal number of mast cells	Zak, Covey, and Snodgrass (1957)
16	8	M	8 years	+	None	None	Haemoglobin 80%. White cells 8,100/cu. mm.; neutrophils 49%; lymphocytes 32%; monocytes 16·5%; eosinophils 1·5%; basophils 1%. Marrow normal	None	Developed acute leukaemia. Biopsy of inguinal gland showed marked mast-cell infiltration of cortex. Spleen histology masked by leukaemic transformation, but mast cells were significantly increased	Balbi (1949)
17	2½	F	From birth	None	++	++	Haemoglobin 40%. White cells 11,900/cu. mm.; neutrophils 39%; lymphocytes 58%; monocytes 3%. Platelets 157,800/cu. mm. Bleeding and clotting times normal. Prothrombin time 34%. Marrow: many mast cells (2% of nucleated cells)	Multiple. Thickening and sclerosis of frontal bone. Long bones irregularly widened with loss of normal contour. Phalanges irregular in shape and size	Bleeding tendency into gastrointestinal tract. Liver biopsy showed portal tracts infiltrated with mononuclear cells and eosinophils; moderate numbers of mast cells in portal areas	Rider, Stein, and Abbuhl (1957)
18	5	M	5 years	++	+++	++	Haemoglobin 58%. White cells 20,350/cu. mm.; neutrophils 25%; lymphocytes 74%; monocytes 1%. Platelets normal. Haemorrhagic diathesis. Bleeding and clotting times normal. Prothrombin time more than 120 sec. Marrow: mast cells 25% of nucleated cells. Occasional mast cell seen in peripheral blood film	None	One of twins; other twin not affected. Died from ruptured subcapsular haematoma of liver into peritoneum. Autopsy showed mast-cell infiltration of skin, liver, spleen, lymph-nodes, thymus, marrow, and connective tissue of kidney, lung, and pancreas	Waters and Lacson (1957)
19	35	M	1 year	None	++	None	Haemoglobin 88%. White cells 5,600–10,000/cu. mm.: basophils 3%–9·5%. Marrow very cellular, showing numerous mast cells, and increase in blood basophils	None	Liver biopsy showed many mast cells, but no fibrosis. Patient also had disseminated xanthomata	Asboe-Hansen and Kaalund-Jørgensen (1956)
20	67	F	12 years	None	++	++	Haemoglobin 58%. White cells 4,800/cu. mm.; neutrophils 59%; lymphocytes 33%; monocytes 2%; eosinophils 6%. Platelets 54,000/cu. mm. Bleeding, clotting, and prothrombin times normal. Marrow: normal apart from eosinophilia (13% of nucleated cells)	Generalized	Bone biopsy showed infiltration with mast cells and mononuclear cells. Marrow showed fibrosis and infiltration with mast cells	Havard and Scott (1959)

Haematological changes. No characteristic haematological changes accompany the condition. The Table gives details of the cases with systemic involvement in which a haemorrhagic diathesis (Cases 2, 3, 5, 8, 13, 17, and 18) or lymphomonocytosis (Cases 1, 3, 6, 7, 11, 13, 16, and 18) was a feature. It is perhaps more than a coincidence that two patients in this series developed acute leukaemia (Balbi, 1949; Sagher, Liban, Ungar, and Schorr, 1956). In addition to the cases listed, a haemorrhagic diathesis has been recorded in cases of urticaria pigmentosa without evidence of systemic involvement (Bolgert and le Sourd, 1949; Asboe-Hansen, 1953; Degos, Delort, and Hewitt, 1954; Grüneberg, Kaiser, and Müller, 1955; Rukavina, Dickinson, and Curtis, 1957). Lymphocytosis or monocytosis has also been noted in the apparently pure cutaneous varieties of the disease (Bolgert and le Sourd, 1949; Pages and Quenard, 1950; Konrad and Winkler, 1953; Degos, Delort, and Hewitt, 1954; Grüneberg, Kaiser, and Müller, 1955; Rukavina, Dickinson, and Curtis, 1957).

Course. Systematized urticaria pigmentosa pursues a relatively benign course. One patient with generalized bone changes has been followed up for five years and has shown little change (Sagher and Schorr, 1956); one patient died at the age of 72 years from infection and haemorrhage secondary to pancytopenia (Berlin, 1955); one died of monocytic leukaemia two years after the diagnosis of systematized urticaria pigmentosa had been made (Sagher, Liban, Ungar, and Schorr, 1956). A boy of eight years died of acute leukaemia (Balbi, 1949). A twelve-month-old baby died of gastroenteritis, but had been in poor health since birth (Ellis, 1949). A boy of five years died after rupture of a subcapsular haematoma of the liver (Waters and Lacson, 1957). So far as is known the other patients listed are alive.

Treatment. The number of therapeutic agents advocated in urticaria pigmentosa is an indication of their ineffectiveness. Antihistamines have been recommended by some, particularly for the control of itching (Moynahan, 1950). Others have maintained that they are of no value (Drennan and Beare, 1951). They do not prevent the pathognomonic wheal which follows local irritation (Grupper, 1954). Improvement in several cases of cutaneous urticaria pigmentosa followed prolonged treatment with deoxycorticosterone acetate (Urbach, Jacobson, and Bell, 1954). This improvement was accompanied by a decrease in the heparin-like substances detected in the blood after local irritation of the lesions. Cortisone therapy has produced a striking improvement in the bullae in the bullous type of urticaria pigmentosa, but no change in the underlying lesions (Robbins, 1954). There was some response to corticoid treatment in a patient with a mast-cell tumour (Hissard, Moncourier, and Jacquet, 1951*a*, *b*), but none to cortisone in another patient with systematized urticaria pigmentosa (Bluefarb and Salk, 1954). Intravenous injection of toluidine blue has likewise proved ineffective (Bluefarb and Salk, 1954). Improvement has been reported in cutaneous urticaria pigmentosa with calciferol, with a recurrence on stopping treatment (Fisher, 1954). We observed no such response in our patient, nor was any beneficial effect noted from polymyxin, despite its recorded action of disrupting mast cells (Parratt and West, 1957).

Chlorpromazine has been found to be effective in preventing the hyperaemia and oedema in animals resulting from 5-hydroxytryptamine and histamine release (Benditt and Rowley, 1956), but no data are available about its effect in human beings with urticaria pigmentosa. Irradiation will occasionally reduce the size of the skin nodules, and was temporarily effective in the treatment of a patient with a mast-cell tumour (Hissard, Moncourier, and Jacquet, 1951*a*, *b*). Radiotherapy to the spleen in one patient with systematized urticaria pigmentosa considerably reduced the size of the organ (Touraine, Solente, and Renault, 1933). The bone pain in our patient was relieved by irradiation.

Pathology. The morbid anatomical basis of the disorder is an infiltration of the skin, bone-marrow, liver, spleen, and lymph-nodes with mast cells. In the bone-marrow more primitive forms occur, and the invading cells often lie in the region of the endosteum; as a result of this distribution sternal puncture may fail to aspirate the mast cells. In the marrow, as in other organs, the mast-cell infiltration may be associated with the presence of eosinophils, lymphocytes, or reticulum cells; mast-cell granulomata have been recorded. In the infiltrated tissues a common sequel is increase in fibrous tissue, the consequences of which include myelofibrosis and cirrhosis of the liver. There is little correlation between radiological evidence of bone disease and the ability to demonstrate mast cells in aspirated bone-marrow: it may be that by the time X-ray changes are demonstrable the infiltration is of long standing, and the resulting fibrosis makes successful aspiration difficult. Bone biopsy is the only method of obtaining satisfactory material for study. The pathological picture as revealed by liver biopsy is similar: here again fibrosis may make successful aspiration difficult, and a normal biopsy specimen may be obtained from an infiltrated and fibrotic liver (Berlin, 1955). The histological changes in the lymph-nodes and spleen resemble those already described. Splenic biopsy on one occasion was followed by the appearance of mast cells in the peripheral blood to the figure of 47 per cent. of the total nucleated elements (Hissard, Moncourier, and Jacquet, 1951*a*, *b*).

The mast cell was originally described by von Recklinghausen in 1863, and the characteristic staining reaction was discovered by Ehrlich in 1879. It is a mesenchymal cell of the histiocytic family. Its characteristic feature is the presence of large cytoplasmic granules, which stain metachromatically with such dyes as toluidine blue; it is this feature that gives these cells their resemblance to blood basophils. The similarity is only superficial, and there are morphological and cytogenetic differences.

The functions of the mast cell. The mast cell is thought to elaborate four substances. Evidence in support of these multifarious activities is provided by the observed correlation between the quantity of the particular substance in any tissue and the local concentration of mast cells. The first function described was that of heparin production (Jorpes, 1946). This has been said to explain the perivascular location of the cell (Riley, 1953*a*, 1954*a*, 1955). In spite of the increased heparin production in systematized mast-cell disease, and in the mast-cell tumours of animals (Oliver, Bloom, and Mangieri, 1947), a

haemorrhagic state is uncommon, and when present is more usually the result of liver damage or thrombocytopenia. The heparin must therefore remain within the cell and not be released into the general circulation. The second product is histamine (Riley and West, 1953; Riley, 1953*b*, *c*; Fulton, Maynard, Riley, and West, 1957). This is the basis of the urtication of the skin lesion when rubbed or exposed to heat or cold. Suggestive evidence has been obtained by the demonstration of fluorescent histamine liberators in the mast cell before disruption (Riley, 1953*b*). More recently the presence of 5-hydroxytryptamine in the mast cells has been established (Benditt, Wong, Arase, and Roeper, 1955), and it has been shown that the oedema following mast-cell damage is mediated primarily through this substance (Rowley and Benditt, 1956). These deductions are the results of animal experiments, and the presence of serotoxin in human mast cells is unproved (Sjoerdsma, Waalkes, and Weissbach, 1957). The fourth product is hyaluronic acid (Asboe-Hansen, 1950, 1951, 1952). Granules can be seen emitted from mast cells during connective-tissue repair. Asboe-Hansen suggested that these granules contain the precursor of hyaluronic acid, which he believed to be heparin. Recent opinion suggests that the role of the mast cell may be concerned less with blood clotting than with the maintenance and repair of connective tissue (Riley, 1954*a*, 1954*b*). The mast-cell function most manifest in systematized urticaria pigmentosa is the production of hyaluronic acid and of connective tissue. Although there is good evidence that mast cells contain heparin, histamine, and hydroxytryptamine, there is in this disease little clinical evidence of their excessive production.

The nature of systematized mast-cell disease. In the syndrome described in the present paper the basic anatomical change is a multiplication of mast cells in certain tissues of the body, notably the skin, bone-marrow, lymph-nodes, spleen, and liver. In consequence of this proliferation such secondary changes as cirrhosis of the liver and fibrosis of the bone-marrow may take place, but they are not of primary importance. This pattern of morbid change is familiar, but it is one peculiar to cells of mesenchymal ancestry, and the disorders of which it is characteristic fall into five groups. First, there are the systematized diseases of reticular tissue which, judged by the most rigid histological criteria, are incontestably neoplastic, and to which the generic title of reticulosarcoma may be applied. The second group includes the leukaemias, Hodgkin's disease, and the related complaints; although the traditional microscopic evidences of cancer are lacking, there is no denying that their behaviour has earned them the description of malignant. These diseases may reasonably be called the reticuloses, using that frequently misapplied label to denote 'a group of diseases of reticulum in which proliferation is followed by differentiation into one or several of the possible cell progeny' (Pullinger, 1932). A third group, to which the name reticulosis is equally applicable, comprises those lipoidoses which are apparently accompanied by a disorder of intracellular lipid metabolism—Gaucher's and Niemann-Pick's diseases. The fourth class consists of what were once called the 'storage-reticuloses', in which histiocytic proliferation is clearly a response to some extracellular perversion of metabolism; the hypercholesterolaemic

xanthomatoses provide familar examples. Finally, systematized reactions of reticular tissue are evoked by some infections, and of this perhaps the most striking instance is kala-azar.

There can be little argument about the nature of the systematized mast-cell disease here described: it must clearly fall into one of these five categories. It cannot be regarded as a malignant neoplasm in the more restricted sense; it is obviously not a reaction to infection or to a general metabolic disorder; it must therefore be ranked as a reticulosis of the second or third group. The normal mast cell is the seat of much metabolic activity, but there is no evidence that in this systematized proliferation there is any disturbance or abnormality of these intracellular processes. It appears more rational to include it in the second class, and perhaps the name 'mast-cell reticulosis', while solving no problems of aetiology or pathogenesis, best indicates the nosological position we believe it should occupy.

We are grateful to Dr. R. Kemp-Harper for his description of the radiological appearances, and to Dr. A. G. Stansfield for his histological reports.

Summary

1. The case is reported of a patient with urticaria pigmentosa, which was associated with lesions in the bones, due to infiltration with mast cells, and with enlargement of the liver and spleen.

2. Nineteen other reported examples of this syndrome are reviewed, and its clinical and pathological features described.

3. The nature of the disease is discussed, and the reasons for regarding it as a 'mast-cell reticulosis' are given.

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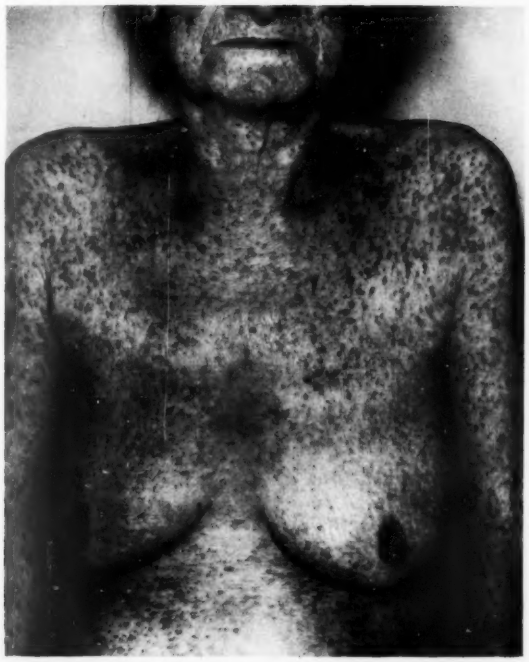

FIG. 1. Photograph to show the characteristic eruption of urticaria pigmentosa

FIG. 2. Skiagram showing the soft-tissue shadow on either side of the lower dorsal vertebrae

FIG. 3. Skiagram of femur, showing mottled increase in density with loss of cortico-medullary demarcation and new bone formation

FIG. 4. Skiagram of upper end of humerus, showing thinning of cortex with patchy increase in density of cancellous bone

FIG. 5. Skiagram of radius and ulna, showing diffuse osteoporosis, with loss of trabecular detail and healing pseudo-fractures

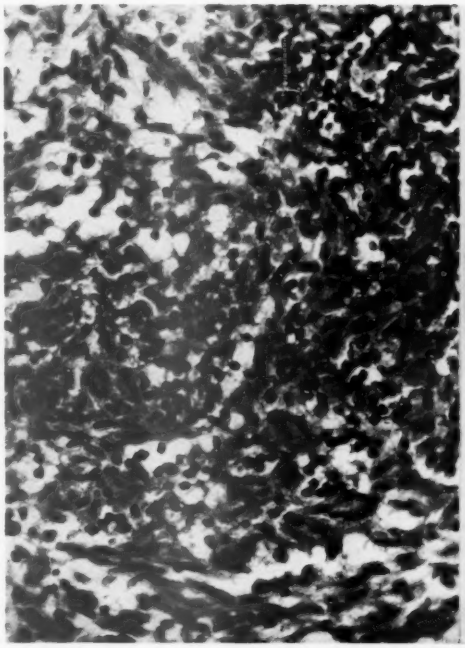

FIG. 6. Photomicrograph of bone biopsy specimen showing mast-cell infiltration in bone marrow (haematoxylin and eosin, ×300)

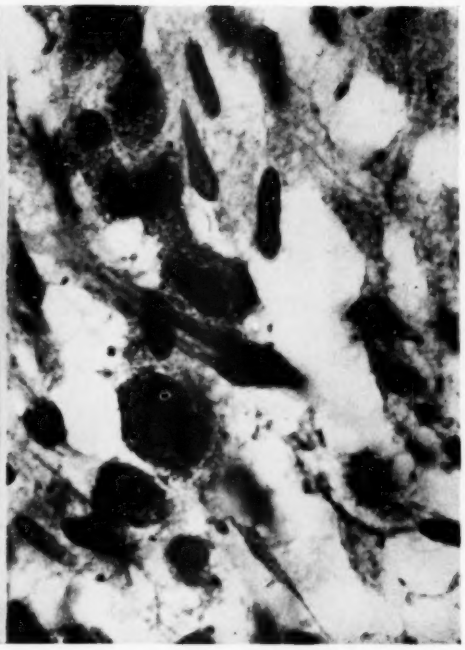

FIG. 7. Photomicrograph of bone biopsy specimen showing details of proliferated mast-cells (haematoxylin and eosin, ×1,000)

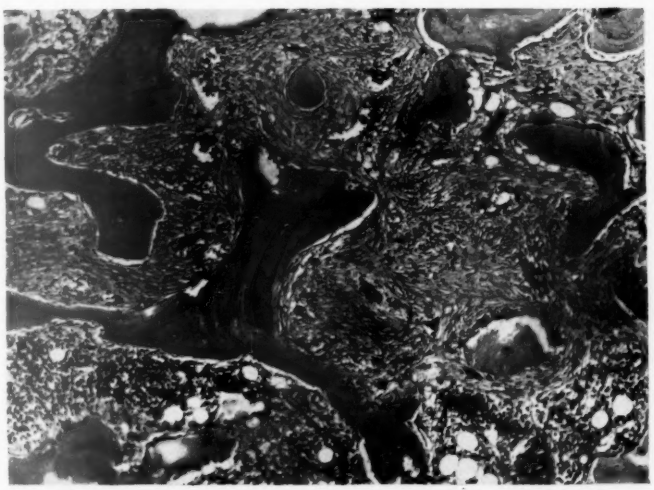

FIG. 8. Photomicrograph of bone biopsy specimen showing fibroblastic proliferation (haematoxylin and eosin, ×65)

616.133–002

GIANT-CELL ARTERITIS[1]

A Review of 35 Cases

By R. W. ROSS RUSSELL

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With Plate 32

It is over 25 years since temporal arteritis was first described, and it has become increasingly clear during that time that the inflammatory process, the cause of which remains unknown, is not confined to the temporal or even to the cranial arteries, but is part of the general vascular disorder, giant-cell arteritis. Nevertheless, the symptoms are so characteristic, and so often confined to the arteries of the carotid system, that the status of cranial arteritis as a clinical entity is undisputed, and the demonstration of lesions in distant arteries has been of more interest to the pathologist than to the clinician. The purpose of the present paper is to review the clinical features of the disease in 35 cases, with particular reference to those with ocular complications and those with evidence of generalized disease, and to assess the effect of steroid therapy at different stages. Twenty-seven patients were studied personally; the remaining eight cases are from hospital records. All were in-patients at some time during the period 1947–58. There were 18 women and 17 men; the oldest was 85, the youngest 59 years old, and the average age 73 years. The diagnosis was made on clinical grounds, and in cases of doubt was confirmed by biopsy of the temporal artery (11 cases). The course of the disease may conveniently be considered in three stages: the stage of headache, the stage of ocular complications, and the stage of systemic complications.

The Stage of Headache

Although many patients complained in retrospect of vague malaise and prodromal pains in muscles and joints for weeks or months, they seldom came under medical care before the onset of headache. Headache was present in all cases, and in only two was it a minor symptom. The pain was unilateral or bilateral, usually appeared in the space of a few hours, and soon became severe. Patients recognized its situation in the scalp and over the temples rather than inside the cranium. It had a constant intense boring quality, with occasional stabbing pains along the course of the vessels. Aspirin usually gave some relief. More

[1] Received September 17, 1958.

characteristic was tenderness of the scalp over the inflamed arteries. Patients frequently remarked on the discomfort of brushing the hair, and even resting the head on a pillow was at times unbearable. So persistent and severe did the headaches and scalp tenderness become that the patient was sometimes denied all sleep, and spent much of the night sitting up in bed, with hands over the face or with the head wrapped in a shawl. Red, tender nodules over the temporal arteries were often noticed and referred to as 'varicose veins'. Symptoms in the lower jaw were also frequent, an early feature being inability

TABLE I

Clinical Features in the Stage of Headache

(35 patients)

Symptoms:	Headache (severe)	33
	Headache (slight)	2
	Tender scalp	34
	General malaise	34
	Loss of weight	25
	Anorexia	24
	Insomnia	21
	Muscular pain	20
	Excessive sweating	15
	Pain on eating	16
	Indigestion	12
	Depression	7
	Vertigo	7
	Sore throat	6
	Diplopia	5
	Mental confusion	4
	Epistaxis	2
Signs:	Tenderness of temporal arteries	32
	Absent pulsation	8
	Diminished pulsation	21
	Fever	29
	Necrosis of scalp	1

to open the mouth because of pain and stiffness in the area of the temporo-mandibular joint. This went on to an aching pain in the side of the face, brought on by chewing and relieved by rest, or to a sensation of tiredness in the jaw on eating. Pains in the muscles and joints were not uncommon during the stage of headache, but were variable in severity. Back, shoulders, neck, and hips were the areas most affected. Other features which were common, but less useful in diagnosis, were mental changes (chiefly confusional or depressive states), fever, excessive sweating, and dyspepsia. As a result of anorexia, malaise, and difficulty in mastication, the patient was usually pale and wasted. There were few physical signs and, although tenderness of the inflamed arteries was almost constant, and diminution of pulsation on the affected side was noted in unilateral cases, it was unusual for pulsation to be completely absent. Thinning of the hair was often noticeable, and ischaemic gangrene of the scalp occurred in one patient.

Laboratory investigations in the stage of headache. A mild normocytic anaemia was almost constant. Of 28 patients examined, 24 had less than 13 g. of

haemoglobin per 100 ml. The average was 11·8 g. per 100 ml., and the lowest 6·8 g. per 100 ml. The anaemia was resistant to treatment with iron, and persisted for many weeks. The bone-marrow was examined in five cases, and was normal. There was little disturbance of white cells: of 27 patients examined, 18 had total white-cell counts from 5,000 to 10,000 per cu. mm., eight had counts between 10,000 and 16,000 per cu. mm., and one had a count of 3,200 per cu. mm. The average total cell count was 9,500 per cu. mm., and the differential count showed no abnormality. The erythrocyte sedimentation rate was constantly raised, and in untreated patients remained elevated for many months. The initial rate in one patient was 27 mm., in two patients 30 to 49 mm., in 11 patients 50 to 79 mm., in seven patients 80 to 90 mm., and in seven patients more than 100 mm. in the first hour (Westergren method). Plasma proteins were estimated in 12 patients (salt-fractionation method). In eight the total was less than 6·5 g. per 100 ml., the mean for these eight patients being 5·5 g. per 100 ml. Reduction was always at the expense of the albumin fraction, and was greatest in long-standing cases. Total globulin fractions were normal, but electrophoresis showed increased α-globulin in four cases. The cerebrospinal fluid was examined in six cases. In four it was normal and in two there was a slight increase in protein content (45 to 60 mg. per 100 ml.).

The Stage of Ocular Complications

Visual disturbance in giant-cell arteritis may result from an ophthalmoplegia or from vascular lesions in the optic nerve and retina. It is important to distinguish the two causes, as the prognosis is very different.

TABLE II

Ophthalmoplegia

(Five patients)

Case number	*Onset*		*Nerve lesion*	*Duration*
	Character	*Weeks after headache*		
2	Sudden	8	VI complete	8 weeks
13	,,	1	III ,,	6 ,,
14	,,	1	III ,,	4 ,,
16	,,	2	VI ,,	?
24	,,	1	VI incomplete	4 weeks

1. *Ophthalmoplegia* occurred in five patients in the present series (Table II). Diplopia usually appeared shortly after the onset of headache, although in one case it was delayed for eight weeks. The lesion, which was often complete, involved the third or sixth cranial nerve. It appeared suddenly and painlessly, and made a slow recovery in two to eight weeks, a sequence of events suggesting a vascular occlusion. In two cases the ophthalmoplegia was the only complication, while in three it was followed by visual failure. This serious event may go unnoticed: for example, ptosis may mask visual failure in the same eye.

TABLE III

Visual Complications in 16 Patients

Case number	*Eye*	*Onset: Weeks after headache*	*Onset: Character*	*Initial stage*	*Treatment*	*Final stage*	*Residual disability*
1	L	4	Sudden		Steroids		Permanent blindness. Optic atrophy
	R	8	1 week		Steroids		Slow progression to blindness. Optic atrophy
2	R	12	Sudden		Steroids		Progression to blindness in 48 hours. Optic atrophy
3	L	9	Sudden		Steroids		Disk waxy. V.A. 3/60
	R	11	Gradual		Steroids*		Disk waxy. V.A. 3/60
4	R	6	Sudden		Steroids		Disk waxy. V.A. 6/6
7	L	7	Sudden		Steroids		V.A. 6/36 nasal field. Optic atrophy
	R	8	1 week	→	Steroids*		V.A. 6/9 (central). Optic atrophy
10	R	3	1 week		Nil		Disk waxy
11	R	8	1 week		Nil		Optic atrophy
	L	9	2 days		Nil		Optic atrophy
12	L	5	Sudden		Nil		Finger counting in lower temporal quadrant. Disk pale
14	L	2	Sudden		Nil		Optic atrophy
17	R	4	Episodic	→	Steroids	→	Optic atrophy
	L	5	1 day		Steroids		Rapid progression to blindness in 24 hours. Optic atrophy
23	R	6	1 week	→	Steroids		V.A. 6/9. Disk waxy
24	R	3	Sudden		Steroids		Optic atrophy
	L	3	Episodic				Recovery. Some temporal constriction. Disk normal
25	R	4	Sudden		Steroids		Recovery. Disk normal. Visual impairment lasted 48 hours
30	L	2	Episodic	→	Steroids		Optic atrophy
31	L	4	?		Steroids		Optic atrophy
33	L	6	Sudden		Nil		Optic atrophy
	R	6	Sudden	→	Nil		Optic atrophy

No perception of light.

Perception of light only.

Appreciation of hand movements and shapes.

Useful vision.

Steroids: all patients receiving steroids were also treated with anticoagulants.

* Treatment started before onset of visual symptoms.

V.A. = visual activity.

2. *Visual failure* occurred in 16 cases, and details are set out in Tables III and IV. The high incidence of visual involvement (50 per cent.) is probably produced by undue selection, since only patients seen in hospital were studied. The interval between the stage of headache and the first symptom of visual failure varied from two days to nine weeks, with an average of 4·7 weeks. The onset was usually abrupt, and the visual loss was frequently noticed on waking in the morning. It sometimes coincided with an improvement, or even cessation, of the headache. The commonest complaint was of a mist or a brown veil over whole or part of the field of one eye, which became denser in 12 to 24 hours, until there was no perception of light in that area. Other patients noticed a gradual deterioration of visual acuity in the course of a few days,

TABLE IV

Summary of Visual Complications

Eyes affected		23
Onset	Sudden	12
	Gradual	7
	Episodic	3
Initial field loss	Total	9
	Partial	14
Residual loss	Recovery	2
	Blindness	13
	Tunnel vision	4
	Partial loss	4

while a few noticed recurrent episodes of blurring or visual loss, which recovered completely in the course of a few minutes or hours. The visual loss in some cases initially involved the whole field, but more commonly it occurred in a segment of the field—either the upper, the lower, the temporal, or the nasal half-fields, or a single quadrant. Such segmental field loss was at times permanent (three cases) but more often showed a tendency to involve other areas of the visual field within 24 to 48 hours. The patient was then left with an eye which was totally blind, but not infrequently, and particularly in those cases in which the onset of visual symptoms had been gradual, macular vision with normal acuity remained while the peripheral field was lost completely (four cases). In the seven patients who suffered bilateral visual loss the interval between involvement of the first and second eye varied from one day to four weeks.

The visual loss at all stages was much greater than the ophthalmoscopic abnormalities. If the patient was seen within a few hours of the onset of visual symptoms, there was retinal oedema in the area corresponding to the field loss. The retina was paler, more shining, and less distinct than normal. The disk showed a similar oedema; it was yellower than normal, the edge was blurred, and there were sometimes small linear haemorrhages round the margins. In severe cases a cherry-red spot was discovered at the macula. The arteries were thin and bloodless, and in patients with a segmental field loss there was sometimes distinct narrowing in the calibre of the branches supplying the affected area of the retina. By contrast the veins were distended, beaded, and irregular, and transient fragmentation or venous streaming was occasionally

observed. Within a few days or weeks, however, many of the abnormal signs disappeared. The retina regained its normal colour and texture, the veins returned to normal, and the cherry-red spot faded. The only lasting abnormalities were in the arteries, which tended to remain attenuated, and in the disk, which gradually became pale and waxy, the final state in severe cases being one of secondary optic atrophy. Plate 32 illustrates the typical ophthalmoscopic appearance in early and late stages.

Any complaint of visual deterioration in cranial arteritis carries a grave risk of permanent loss of sight in the affected eye. Of 23 eyes affected only two regained useful vision, and 13 were completely blind. Tunnel vision was retained in four eyes, but was still a grave disability.

Treatment

Prior to 1952–3 patients were treated symptomatically with salicylates in various forms, but since that time the majority have received steriods, either as cortisone, in an initial dose of 100 to 300 mg. per day, or as prednisone, 10 to 50 mg. per day. The effect of steroids may be inferred by comparing the

TABLE V

Effect of Steroids in Patients Without Eye Complications

	Steroids	*Salicylates*
Total number of patients	10	13
Developed visual failure	0	5

results in patients treated before and after 1952–3. Twenty-three patients had normal vision in the stage of headache, and of these 10 received steroids, and 13 symptomatic treatment. Steroids were more effective than salicylates in reducing fever and relieving headache. Table V shows the incidence of ocular complications during treatment. Visual failure did not occur in the steroid-treated group, but developed in over one-third of the salicylate group. The

TABLE VI

Effect of Steroids and Anticoagulants in Patients with Established Visual Failure

	Steroids	*Salicylates*
Total number of patients	11	5
Total number of eyes affected	16	7
Number of eyes improved	2	0
Number of eyes unchanged	6	3
Number of eyes which deteriorated	8	4

total number of patients with visual failure was 16 (23 eyes affected). Eleven of these patients received combined steroid and anticoagulant treatment after visual failure had occurred, and five received salicylates. Two eyes in the steroid group showed improvement, but in the remainder steroids appeared to have no effect on the progression of the ocular lesion, or on the final result (Table VI). In two patients with unilateral symptoms who were treated with steroids visual failure occurred in the second eye during treatment.

Stage of Systemic Complications

A careful follow-up study was made of 28 patients for periods of six months to 10 years after the onset of the disease. Twenty-one patients made a satisfactory return to normal health in six to 18 months. During this time loss of weight, fatigue, muscle weakness, joint pains, and occasional headache persisted in many patients, and the erythrocyte sedimentation rate remained elevated. When the disease eventually subsided, the subsequent medical histories of these patients were not remarkable. Arteries which had been inflamed returned to normal, and where pulsation had been absent it was restored. There was no improvement in the visual state. In seven patients, however, the disease assumed an atypical form, and various complications appeared immediately after the headache or after a latent interval. Some of these complications were due to arterial occlusion, others to a generalized systemic disturbance of muscles and joints. A study of these aspects of the disease is of importance, because patients may be seen for the first time at a late stage, and the characteristic history of headache may be obtained only by careful questioning. Two patients showed evidence of generalized arteritis, with lesions in viscera and skin (Cases 31 and 17), two developed an isolated neuropathy probably of vascular origin (Cases 22 and 33), and three presented a syndrome of crippling backache, muscle pain, and weakness (Cases 32, 34, and 35).

Case 31. A woman aged 75. Temporal arteritis; ophthalmic arteritis; mesenteric arteritis; hemiplegia; cardiac failure; death.

This patient began to experience severe temporal headaches in October 1955. The pain was felt most on the left side, and extended on to the side of the face. Her scalp was tender, and chewing was almost impossible because of aching in the jaw muscles. After about four weeks she lost the use of the left eye, but failed to notice it for some days, by which time the eye was completely blind. Examination two months after the onset of symptoms showed a tender, thickened temporal artery on the left side, with absent pulsation. The left optic disk was pale and slightly swollen, with a few small surrounding haemorrhages; the arteries were thread-like, and the veins full. The pulse was regular, blood-pressure 215/120, erythrocyte sedimentation rate 31 mm. in one hour (Westergren), haemoglobin 80 per cent. (Haldane), and white cells 8,200 per cu. mm. Treatment was started with cortisone, in a dose of 125 mg. per day, combined with anticoagulants, and within a few days the headaches were relieved. Ten days later, in December 1955, the patient developed upper abdominal pain and vomiting, with diffuse abdominal tenderness. The pain increased in severity for 48 hours, and her general condition deteriorated. At laparotomy a length of small bowel was found to be gangrenous and was removed, and an end-to-end anastomosis performed. Steroids were stopped during the operative period, but resumed five days later. Healing of the abdominal wound was slow, and was complicated by a faecal fistula. The erythrocyte sedimentation rate fell to normal two weeks after operation. One month later she awoke with a mild right hemiparesis, from which she recovered during the course of a few days. Pulsation in the left common carotid was observed to be less than on the right. The erythrocyte sedimentation rate

remained normal, and there was no recurrence of headache. Two months later she had an episode of pulmonary oedema, and from that time suffered intermittently from heart failure until her death 18 months later.

Examination of material removed at operation showed thrombotic infarction of the gut secondary to necrotizing arteritis. The histological report on sections of the superior mesenteric artery (Dr. R. Shorter) was as follows: 'The section consists of fatty connective tissue showing congestion and subacute inflammation with early fibrosis. The fat includes a small lymph-node showing chronic inflammation and some vascular channels. The two largest vessels are arteries occluded by recently formed thrombus. There is considerable destruction of media with infiltration by fibrin; in places the muscle fibres have completely disappeared. The internal elastic lamina is visible for only part of the circumference in both vessels. There are only very occasional inflammatory cells in the media of the vessels, and no histiocytes or giant cells in relation to elastica. The adventitial fibrous tissue shows considerable mesoblastic activity and at one point in one vessel, where the wall is entirely fibrinoid, the mesoblastic cells penetrate into the wall and are more hyperchromatic than elsewhere, some cells having two or three nuclei. A vena comes shows oedema of its intima and thin muscular coat, and is infiltrated by a few inflammatory cells including polymorphs. There is no thrombus in the lumen.'

Comment. This is the only record of mesenteric thrombosis in the course of cranial arteritis, although microscopic evidence of involvement of the mesenteric arteries has been reported (Harrison, 1948). The histological findings in the present case were those of a severe type of arteritis with a few giant cells; the appearance was not typical of giant-cell arteritis, but was similar to that seen in polyarteritis nodosa. The occurrence of cerebral thrombosis in the course of the illness cannot be ascribed to arteritis, as no histological material was available, and thrombosis from atherosclerosis and hypertension was a likely event in such a patient. Diminished pulsation in the common carotid has not been reported previously in cranial arteritis, although the artery has been found to be involved at autopsy (Heptinstall, Porter, and Barkley, 1954).

Case 17. A man aged 64. Temporal arteritis; bilateral central retinal artery thrombosis; pneumonia; polyarthritis; purpura; melaena; dementia; hypertensive cardiac failure; death.

The patient was admitted to hospital on 7.1.54 complaining of headache and visual disturbance. The past and family history were negative, apart from one brother who suffered from arteriosclerotic gangrene of the foot. The patient had been in good health until five weeks previously, when he had severe pain in the back of the neck. The pain spread upwards to the occipital region, and he felt tender lumps at the back of his head. In addition he suffered from loss of weight, insomnia, repeated epistaxis, and deterioration in memory. Pain in the jaw occurred with eating. Visual symptoms had been present for one week, and consisted at first of transient loss of the lower half of the right visual field for a few minutes at a time. One week later he noticed blurring of vision in the periphery of the left visual field, and the following day he woke up completely blind in the left eye. At the same time the vision in the right eye deteriorated again, and he was able to see only a small area in the centre of the field.

On examination he was ill, wasted, and mildly febrile (temperature 99° F). The left eye was completely blind, but central visual acuity of 6/18 was retained

in the right eye. The optic disks were slightly swollen, and surrounded by small retinal haemorrhages. All the arteries were thread-like, and the veins were grossly congested. The pupils were dilated and unreactive, and there was some defect of conjugate ocular movement to the right. There were no other abnormal signs, and the blood-pressure was 170/70. The temporal arteries pulsated normally, but tender swellings were found over the occipital arteries. The clinical diagnosis was cranial arteritis. X-rays of the skull and chest, electroencephalography, and lumbar puncture showed no abnormality. The haemoglobin was 92 per cent. (Haldane), white cells 11,700 per cu. mm., and erythrocyte sedimentation rate 85 mm. in one hour (Westergren).

He was treated with cortisone by mouth, in a dose of 200 mg. per day, reduced to 150 mg. per day after four days. Anticoagulants (phenindione) were given in full dosage. Immediate relief of headache was produced. During the first week there was no visual improvement. The retinal arteries remained thin, and fragmentation of the column of blood was observed in the veins round the optic disk. The disks became gradually paler and atrophic. After four weeks in hospital, when the cortisone was reduced to 75 mg. per day, he again became febrile and complained of headache, and the dose was raised to 150 mg. per day. He was discharged after six weeks, although the erythrocyte sedimentation rate was still raised (38 mm.). A small area of central vision was preserved in the right eye, and acuity was 6/9. He was seen at monthly intervals, and the vision in the right eye gradually deteriorated, until he became totally blind nine months later. In August 1954, after a reduction in the dose of cortisone, he experienced a return of headache and malaise, and began to lose weight; the erythrocyte sedimentation rate rose from 10 mm. to 48 mm. The symptoms settled when the dose of cortisone was increased. In September 1954 he developed lobar pneumonia in the left upper lobe, but recovered satisfactorily after treatment with chlortetracycline. Cortisone was continued.

In November 1954, 11 months after the start of his illness, he developed pain and swelling of the small joints of both hands and feet, elbows, and wrists. This was accompanied by a purpuric rash over the legs, buttocks, back, and arms, and two days later by colicky abdominal pain and melaena. Improvement occurred when the dose of cortisone was raised to 200 mg. per day. In January 1955, one year after the initial illness, he was fairly well, and complained only of general stiffness. Occasional purpuric spots were visible, and he was quite blind. The erythrocyte sedimentation rate was 28 mm. in one hour, and cortisone was continued (150 mg. per day). During 1955 he was twice in hospital, once with bronchopneumonia and once with congestive cardiac failure. He recovered well on both occasions. In 1956 he was again in hospital with left ventricular failure. Prednisone was substituted for cortisone. Any attempt at stopping or reducing steroid therapy led to an immediate return of arthritis, headache, and malaise.

In June 1957 he was admitted with vague malaise, sweating, and loss of weight, thought to be due to exacerbation of the arthritis. Steroids were increased, but this measure precipitated an episode of acute paranoid dementia. On stopping all treatment the polyarthritis returned, and a 'butterfly' rash appeared on the face. The mental symptoms resolved in a few days. He continued to complain of breathlessness and oedema of the legs, and eventually died in an acute attack of left ventricular failure in October 1957, almost four years after the onset of his illness.

Comment. The acute purpuric illness resembled the Henoch-Schönlein syndrome, and was similar in some respects to Case 31. The mental symptoms

were attributed to cortisone, but have been noted frequently in patients not treated with steroids (Cooke, Cloake, Govan, and Colbeck, 1946). The terminal illness, with polyarthritis, 'butterfly' rash, and hypertension, had some features in common with systemic lupus erythematosus.

Case 22. A man aged 74. Temporal arteritis; lateral popliteal palsy; deep venous thrombosis; recovery.

This patient was in good health until June 1957, when he experienced the sudden onset of supraorbital headache, which concentrated over the next few days in a tender area over the right temple. He felt generally unwell, with aching in the small joints of the hands, anorexia, and slight fever. He was seen during the third week of illness, when the temporal arteries were found to be beaded and tender. Arterial pulsation was present, though reduced. Visual acuity was unchanged, and the fundi normal. The erythrocyte sedimentation rate was 90 mm. in one hour (Westergren). Treatment was begun immediately with large doses of steroids (prednisone 15 mg. thrice daily), and within a short time headache and malaise were completely relieved. After a week, however, he began to experience epigastric pain after food and during the night. He was admitted to hospital, where a barium meal showed a duodenal ulcer. Prednisone was accordingly reduced to 5 mg. thrice daily, and he was maintained on this dose as an out-patient. The dyspepsia responded to symptomatic treatment.

In August 1957, eight weeks after the onset of the illness, he suddenly had painless foot-drop on the right side. Examination showed weakness of the right anterior tibial and peroneal muscles, without sensory loss or reflex change. The arterial pulses in the legs were present and equal. Electromyographic studies confirmed the presence of a lateral popliteal palsy, with signs of partial denervation in the corresponding muscles (reduced electromyographic pattern on volition, and spontaneous fibrillation at rest). Power in the affected muscles returned slowly during three months. Two months later the right leg suddenly began to swell after exertion. The swelling was painful and extended to the mid-thigh, and a tender thrombotic popliteal vein was palpable behind the knee. Treatment consisted of rest and elevation of the legs for three weeks. The oedema subsided in four months. Prednisone was continued (5 mg. thrice daily). Eight months after the onset of the illness he omitted to take the tablets, and next day noticed a return of headache and malaise, with dizziness on walking. These symptoms were quickly relieved by steroids. He continues to take a small regular dose (5 mg. twice a day). Pulsation of the temporal arteries is normal.

Comment. The sudden onset of lateral popliteal paresis, followed by gradual but complete recovery, is suggestive of an ischaemic lesion affecting the nutrient artery of the nerve. The time of onset (two months after the initial headache) was later than in Case 33, and there was no pain. Venous thrombosis has been reported occasionally (Crosby and Wadsworth, 1948), but the onset immediately following exercise, as in the present case, is unusual.

Case 32. A woman aged 67. Cranial arteritis; chronic course with muscle weakness; recovery.

The patient first noticed general lassitude, fever, headache, and scalp tenderness in the summer of 1954. Other features of her illness were loss of

weight, vague joint pains, and excessive sweating. The striking feature on examination was prominence, irregularity, and tenderness of both temporal arteries. Her temperature was 100·2° F. She was anaemic (haemoglobin 53 per cent. (Haldane)); the erythrocyte sedimentation rate was 126 mm. in one hour (Westergren), and plasma proteins 4·8 g. per 100 ml. (albumin 3·0 g., globulin 1·8 g.). Treatment was begun with cortisone in moderate doses (50 mg. twice a day), and these were gradually reduced during the next 10 weeks. The headache was improved, and the temperature fell, but she continued to complain of pains in the neck and shoulders. The anaemia was refractory to all forms of treatment apart from blood transfusion. The erythrocyte sedimentation rate fell from 126 to 85 mm., but as the cortisone was reduced her pyrexia returned, and the sedimentation rate again rose. She remained febrile until her discharge five months later.

For the next four years she remained in indifferent health, subject to headaches, recurrent flitting joint pains, and severe muscle weakness in the legs. She was able to walk with assistance, but could not climb stairs. She had marked wasting and weakness of the proximal muscles of both arms and legs, with slight limitation of joint movement by pain. There was no loss of reflexes or sensory disturbance. X-rays showed only mild osteoarthritic changes, and there were no ocular complications. The erythrocyte sedimentation rate showed a slow decline since the initial illness. One year after the onset it was 98 mm. in one hour (Westergren); after two years 50 mm., after three years 18 mm., and after four years 15 mm.

Comment. The evidence in this case indicates that the disease may remain active for as long as four years after the initial headache, the late symptoms being muscular and arthritic. As in Case 34, the severe degree of muscle weakness was out of proportion to the changes in the joints.

Case 33. A man aged 70. Temporal arteritis; bilateral retinal arteritis; ischaemic median neuritis; recovery.

The patient was in good health until July 1957, when he had a sudden onset of severe pain in both temples. The scalp on both sides was tender, and analgesics gave little relief. After six weeks of continuous discomfort, during which he lost weight and felt generally wretched, the pain left him as suddenly as it had begun. Three weeks later, on rising one morning, he noticed that he had completely lost the sight of the left eye. In the course of 24 hours the field of vision of the right eye became constricted, until he was able to see only a small area in the centre of the field. The acuity of vision in this area remained normal. During the period of headache he also noticed an aching pain in the right shoulder, which gradually spread down the arm, and became increasingly severe after the headache abated. The pain had an intense boring, burning quality, and was felt most on the inner border of the arm. It was accompanied by numbness of the radial two fingers and thumb, and by weakness of the whole limb. Steroid therapy, which was begun at the time of the ocular symptoms, had to be discontinued because of severe dyspepsia.

The symptoms in the arm gradually increased in severity for nine months, and he was admitted to hospital in March 1958. At that time he was in continuous discomfort, and any movements of the limb, whether active or passive, were almost impossible because of pain and muscular spasm. There was exquisite tenderness over the neurovascular bundle down the medial side of the upper arm, and the tenderness extended down the flexor surface of the forearm over the course of the median nerve. Although power was reduced in all

groups, there was no muscle wasting. The thumb and radial two fingers were shiny and atrophic, and the finger-nails showed clubbing. All forms of sensation were reduced over the distribution of the median nerve in the hand. In the cranial nerves the left fundus showed optic atrophy, with marked arterial thinning. There was no perception of light, and the direct light reflex was absent. The right disk was pale, but not so pale as the left, and the arteries were attenuated. Visual acuity was 6/12, and the fields were restricted to a small area round the fixation point. All the peripheral pulses were palpable, but were less easy to feel on the right than on the left side. The skin temperature was equal on both sides. X-rays of the chest, cervical spine, and right shoulder showed no abnormality apart from mild osteoarthritic changes. The haemoglobin was 109 per cent. (Hadane), white cells 9,700 per cu. mm., erythrocyte sedimentation rate 30 mm. in one hour (Westergren), and serum proteins 7·2 g. per 100 ml. (albumin 4·2 g., globulin 3·0 g.). Measurement of blood-flow in the right forearm showed no difference from the normal side. Muscle biopsy (right biceps) showed no abnormality, and no evidence of arteritis.

Treatment consisted of rest in bed, and codeine phosphate by injection for the pain. The patient was intolerant of aspirin by mouth, and an attempt to start steroid therapy once more induced severe dyspeptic symptoms, and was discontinued. At the end of March 1958, nine months after the onset of symptoms, the pain in the arm began to improve, and within a week he was able to move it without discomfort. All pain had vanished in two weeks, and he was discharged.

Comment. The illness in this case was dominated by a syndrome resembling post-traumatic causalgia of the median nerve on one side, and consisting of intense pain and tenderness, with a median sensory impairment and trophic changes in the fingers. The cause is likely to have been an ischaemic median neuritis due to reduction of the arterial supply to the nerve.

Case 34. A man aged 67. Cranial arteritis; muscle wasting and weakness; recovery.

The patient was alert and active until February 1958, when he developed severe and persistent bilateral headache. His scalp was so sensitive that he gave up brushing his hair, and he noticed tortuous and beaded blood-vessels on his temples, which were especially tender. Other features of his illness were slight fever, excessive sweating, anorexia, loss of weight, and inability to open his mouth fully. He had some pain and stiffness in the joints and muscles at this stage, and walking was a discomfort. After a month, as the headache subsided, the skeletal pains became worse. There was a constant aching in the muscles of the pelvis and shoulders, which was made worse by movement and eased by rest. Pain was accompanied by stiffness, especially in the mornings, and by weakness of the muscles. He became unable to rise from a chair without help, and walked only with the greatest difficulty and discomfort. There was no sensory loss or paraesthesia, the hands and feet remained unaffected, there was no disturbance of speech or swallowing, and the eyesight was normal

Examination at this stage showed a pale, enfeebled patient, who was bedridden. Both temporal arteries were palpable, and the scalp was not tender. The cranial nerves and optic fundi were normal. In the upper limbs there was marked wasting, weakness, and tenderness of all the muscles of the shoulder girdle and upper arms on both sides, especially the left. The forearms and hands were normal. The hip and shoulder joints could be moved passively through

a full range, although there was some discomfort at extremes of movement. Tone, co-ordination and sensation were not affected, and the reflexes were brisk and equal. There was loss of power in the abdominal muscles, and the patient could not sit up unaided. The abdominal reflexes were absent. In the legs there was wasting and weakness of quadriceps, glutei, and hamstrings on both sides. The calf was affected on the left, but not on the right. The knee-jerks were brisk and equal, the ankle-jerk was reduced on the left, and both plantar responses were flexor. Other systems were normal. The blood-pressure was 140/90, haemoglobin 85 per cent. (Haldane), white cells 6,100 per cu. mm., erythrocyte sedimentation rate 72 mm. in one hour (Westergren), and plasma proteins 6·2 g. per 100 ml. (albumin 4·2 g., globulin 2·0 g.). Electromyographic exploration and biopsy of the wasted muscles showed no abnormality. A small muscle artery showed no evidence of inflammation. All the skeletal symptoms were relieved at once by steroids (prednisone 40 mg. per day). Within 24 hours the patient could walk unaided, and in a week he could climb stairs. The erythrocyte sedimentation rate fell to 20 mm. after two weeks. Steroids were continued.

Comment. This patient presented skeletal symptoms only, and the diagnosis was in doubt until he described the characteristic headache and scalp tenderness at the onset of the illness.

Case 35. A man aged 64. Cranial arteritis; subacute course, with muscle weakness. Death from bronchopneumonia.

In March 1957 the patient, having been in perfect health the night before, awoke one morning with generalized muscular pain. The pains were in the muscles of the back, arms, and thighs; he was unable to sit up in bed because of stiffness. The muscles were acutely tender. The following day he noticed, in addition, an aching pain in the jaw muscles and over the temples. He found difficulty in opening his mouth. In the course of a week tender lumps appeared over both temporal arteries, and the scalp was painfully sensitive to the lightest touch. He remained in bed, unable to move, for two weeks, but then improved sufficiently to be able to move painfully about the house. The headache abated in a few weeks, but the skeletal symptoms remained severe. One year later he was still complaining of pain in the lower back and thighs; he was unable to rise from a chair because of muscle pain and weakness, and used to progress upstairs backwards in the sitting position. All the symptoms were worse in the mornings, and were eased slightly by hot fomentations. He lost a stone in weight, and had occasional headaches, but noticed no fever. During this time he was diagnosed successively as suffering from renal stones, osteoarthritis of the spine, carcinoma of the prostate, rheumatism, and anxiety neurosis.

Fourteen months after the onset he was admitted to hospital, and was found to have generalized wasting, with weakness of the muscles of the trunk, thighs, and shoulders. The muscles were acutely tender, but there was no abnormality of the nervous or cardiovascular systems. His temperature was 101° F, haemoglobin 52 per cent. (Haldane), white cells 3,200 per cu. mm., erythrocyte sedimentation rate 119 mm. in one hour (Westergren); and plasma proteins 6·9 g. per 100 ml. (albumin 3·3 g., globulin 3·6 g.). Electrophoresis showed increased a_1 globulin. There was slight limitation of movement of the shoulder, hips, and back, but no X-ray changes. Electromyographic examination gave no evidence of denervation, but on stimulation there was abnormal scattering of the motor unit activity spread over 20 m-seconds. This phenomenon is seen

in some cases of myositis. Within 12 hours of receiving steroids (prednisone 40 mg. per day) he could get out of bed and climb stairs without discomfort. In three days the erythrocyte sedimentation rate fell to 50 mm., and in a week to 10 mm. Steroids were continued for a year until the patient died suddenly from bronchopneumonia.

Comment. As in Cases 32 and 34, the proximal limb muscles were those most severely affected. An inability to climb stairs due to quadriceps weakness was common to all three patients.

Discussion

Giant-cell arteritis is essentially an inflammatory condition which results in partial or complete occlusion of a number of arteries, but which is capable of complete resolution and return to normal. Arteries such as the scalp vessels, which have been occluded during the phase of headache, are found to pulsate normally when the patients are examined after the disease has subsided, and the subsequent medical histories of these patients follow the normal pattern for elderly subjects. Clearly a state of arterial insufficiency, even if it is only temporary, may be a serious event when it involves important areas. In the eye the granulomatous inflammation which occurs in the ophthalmic arteries (Cardell and Hanley, 1951) may subsequently return to normal (Heptinstall, Porter, and Barkley, 1954), but the nervous system is unusually sensitive to anoxia, and a temporary diminution of blood-supply may be sufficient to cause neuronal atrophy and permanent loss of function. For this reason the ocular complications of giant-cell arteritis are by far the most important, and this fact is confirmed by the present report. Similarly, narrowing of the coronary arteries by giant-cell inflammation may precipitate myocardial infarction, an event which is not uncommon in the first few months of the illness (Kilbourne and Wolff, 1949), although it did not occur in the present series.

It is fortunate that ophthalmic arteritis is almost always preceded by the characteristic syndrome of temporal arteritis, because it may be possible to anticipate the visual complications, and perhaps prevent them, by early diagnosis and correct treatment. The present report shows that symptoms of special diagnostic value are scalp tenderness, difficulty in opening the mouth, and pain on eating, which may be due to ischaemia of the muscles of mastication. It is important to note that pulsation in the affected artery is not necessarily absent, and that a number of arteries may be occluded simultaneously, as shown by the occurrence of ischaemic necrosis of the scalp. A normal white-cell count was found in the majority of patients in the present series, although a polymorphonuclear leucocytosis is often mentioned as a constant feature of the illness. The difficulties of early diagnosis, however, may be formidable, and many patients must inevitably be seen only after the onset of visual failure, an event which is unfortunately often of sudden onset. It was uncommon in the present series for the patient to have prodromal symptoms such as transient blurring or amaurosis, although this has not been the experience of other

authors (Meadows, 1954). There has been much speculation as to the precise site of inflammation in the arteries of the eye, and two clinical syndromes have been described according to whether the arteries to the retina or to the optic nerve are affected (Wagener, 1946; Bruce, 1950). The distinction is a fine one, since the axial vessels of the optic nerve, supplying its central portion, are direct branches of the central retinal artery (Hughes, 1958). The cases in the present series show that the initial visual loss is often altitudinal or segmental, suggesting that the lesion at this stage may be in a retinal branch artery—although similar field defects may occasionally result from optic nerve lesions (Hughes, 1958). Branch occlusion has been observed directly (Parsons-Smith, 1952), and a variation in calibre between different branches of the retinal artery is not uncommon.

The ophthalmoscopic findings may be influenced not so much by the site of the arterial occlusion as by the speed with which it occurs. In giant-cell arteritis the reduction in size of the arterial lumen is usually a result of intimal proliferation—presumably a slow process,—while actual thrombosis is unusual (Heptinstall, Porter, and Barkley, 1954). Thus a rapid occlusion, probably thrombotic, in the central retinal artery produces the appearance of a pale oedematous retina with a cherry-red spot at the macula. Such an event occurs in only 8 per cent. of cases (Meadows, 1954), and it is commoner for occlusion to take place gradually without thrombosis. The ophthalmoscopic changes are then much less marked than in rapid occlusion, and consist of slight retinal oedema, which may be difficult to recognize, and transient swelling of the disk progressing slowly to optic atrophy. Complete blindnesss of one or both eyes is the commonest end-result reported in the literature (Bruce, 1950), and an unusual feature of the present series is the frequency of tunnel vision, previously infrequently recorded (Johnson, Harley, and Horton, 1943). It is probably due to a retino-ciliary anastomosis at the macula at an arteriolar or capillary level (since none of the patients had a visible retino-ciliary artery at the disk). It is possible that, if the retinal artery is occluded slowly, the anastomosis has more time to develop and macular sparing is more likely to occur. Changes in the retinal veins have been described occasionally (Horton and McGath, 1937; Bruce, 1949), and it is difficult to understand why they should appear distended or irregular after arterial occlusions, since the blood-flow through them has been diminished. This appearance of the veins, and the transient streaming of blood through the central part of the lumen which may sometimes be seen, suggest that partial thrombosis is taking place. This thrombosis may be the result of phlebitis, which is known to occur in other situations (Case 31). Fragmentation of the venous blood has been ascribed to hyperglobulinaemia (Roux, 1954), but no patient with increased serum globulin was found in the present series. Reduction of serum albumin, which is not uncommon, probably results from reduced protein intake, and is proportional to the length of the illness.

Although there are reports of patients with moderately severe visual loss making a good recovery without treatment (Johnson, Harley, and Horton, 1943)—and this occurred in one patient in the present series,—the majority

of patients are left with severe and permanent impairment of sight. It is of great importance to know whether steroids, which are so effective in controlling the constitutional effects of the disease, can also benefit patients with visual involvement. Previous authors (Birkhead, Wagener, and Shick, 1957) have detected some improvement in a few patients treated after partial visual loss, but once the eye is blind steroids are ineffective. It seems likely from the present report that steroids given before the onset of visual symptoms prevent the spread of the disease to the eyes, but the view is confirmed that they have little effect on the progression of an ocular lesion once it has occurred, and that a second eye may become involved during treatment. It is suggested, therefore, that all patients with giant-cell arteritis should receive steroids as soon as the diagnosis is made, and for some months afterwards. The longest recorded interval between headache and visual involvement is six months (Wagener and Hollenhorst, 1958),[2] and steroids should therefore be given for a minimum of six months, and regulated according to the clinical state of the patient, the temperature chart, and the erythrocyte sedimentation rate. Large doses (30 to 50 mg. of prednisone) may be required to control headache and constitutional disturbance during the first few weeks, but may later be reduced to a maintenance dose of 10 to 20 mg. per day. If visual symptoms have already occurred, or if there is clinical evidence of the spread of arteritis beyond the scalp vessels (for example, ophthalmoplegia), it seems advisable that the patient be admitted to hospital at once and treated with anticoagulants as well as steroids, even though there is no proof that combined treatment is any more effective than steroids alone. Any return of headache or constitutional symptoms during treatment indicates that the dose has fallen below an effective level and should be increased. After six months steroids may gradually be discontinued in the majority of cases, but in patients with partial visual loss it may be wise to continue a small dose for a further year. In bilateral cases the second eye is commonly affected within a few days or weeks of the first. After two months the chances of this occurrence are slight (Wagener and Hollenhorst, 1958).

The occurrence of giant-cell arteritis in vessels outside the carotid system is well known, and, although such lesions may be found in the limb arteries *post mortem*, they seldom give rise to symptoms during life. A temporary partial or complete occlusion of peripheral arteries may, however, be detected during the acute phase (Jennings, 1948; Case 33 of the present series). In the legs symptoms of intermittent claudication are rare, possibly because the patients are usually too old or infirm to walk far, but gangrene has been reported on two occasions (Frangenheim, 1951; Finlayson and Robinson, 1955).

Involvement of peripheral nerves has not been previously reported; two patients in the present series had widely different symptoms, but in both cases an ischaemic aetiology is likely. In Case 22 the sudden painless onset of

[2] Since this paper was submitted one patient (Case 26) has developed central retinal venous thrombosis two years after the onset of headache. The onset coincided with a reduction in steroid dosage, and was accompanied by fever, general malaise, and elevated erythrocyte sedimentation rate.

complete lateral popliteal palsy, with subsequent slow recovery, suggests a thrombotic occlusion of a nutrient vessel, a sequence of events not uncommon in polyarteritis nodosa. The patient was receiving steroids at the time. The other patient (Case 33) experienced an intensely painful causalgia-like lesion of the median nerve. This occurs in situations where the blood-supply to a nerve is reduced gradually or by a series of small episodes, and has been explained by the mechanism of artificial synapse (Doupe, Cullen, and Chance, 1944). It is suggested that defective insulation occurs in the nerve trunks, and impulses which are constantly passing down sympathetic fibres are thus able to stimulate afferent pain fibres. The occurrence of peripheral neuritis in the course of giant-cell arteritis, although it is due to ischaemia, does not appear to carry the same poor prognosis as in the eye. The complication may be painful, but full return of function appears to occur, and the disease subsides in the usual way.

Cases showing evidence of visceral arteritis are of particular interest, and the occurrence of two such cases in a relatively small series suggests that this complication cannot be as rare as has been supposed. Both cases began with clear clinical evidence of temporal and ophthalmic arteritis, followed after a latent interval by signs of disease elsewhere. In Case 31 there was no indication of widespread arteritis until three months later, when a sudden mesenteric thrombosis occurred. The patient was receiving steroids at the time. Resection of the affected area of gut was followed by satisfactory recovery, suggesting that the inflammation was local, and that other arteries in that area were relatively normal. There were no further visceral symptoms. In Case 17 the symptoms were more varied. The stage of ocular complications was followed by a latent period of 10 months, and then by further constitutional disturbance, with polyarteritis, purpura, and melaena, resembling the Henoch-Schönlein syndrome seen in other generalized vascular disorders of unknown cause. This relapse appeared to be controlled by an increased dose of steroids, but the patient continued to show evidence of widespread disease (polyarthritis, rash, mental disturbance, and a raised erythrocyte sedimentation rate) until his death three years later. The absence of visceral lesions has previously been thought to be a feature of giant-cell arteritis, although they occur not infrequently in polyarteritis nodosa (Miller and Daley, 1946). Many clinical features of the above two cases are common to giant-cell arteritis and polyarteritis nodosa, and cast doubt on the distinction which is drawn between them, a distinction which cannot always be upheld with certainty even on histological grounds (Cooke, Cloake, Govan, and Colbeck, 1946). Case 31, for instance, began with clinical evidence of temporal and ophthalmic arteritis, but the histological appearances in the mesenteric artery were similar to those of polyarteritis nodosa. Evidence of renal involvement, as shown either by abnormal urinary findings in life or by microscopic evidence of arteritis *post mortem*, while a common feature of polyarteritis, appears to be extremely uncommon in giant-cell arteritis. This may account partly for the difference in prognosis between the two conditions.

While it is recognized that joint and muscle pain may occur in the prodromal

period and during the acute phase (Brown and Hampson, 1944), the syndrome of chronic myalgia and arthritis following cranial arteritis has received insufficient attention. The fully developed state is illustrated by the three cases reported above. After a characteristic attack of temporal arteritis, severe pain and weakness developed in the muscles of the limb girdles and trunk, accompanied by limitation of movement in the shoulders, hips, and spine. The patients were severely incapacitated, and had fever, sweating, anaemia, and loss of weight. Steroid therapy in two patients (Cases 34 and 35) brought about a rapid improvement, with disappearance of muscle pain and stiffness and decline in the erythrocyte sedimentation rate, but in the untreated patient (Case 32) the symptoms persisted for four years. An identical clinical syndrome, with similar changes in erythrocyte sedimentation rate, haemoglobin, and serum proteins, has been previously described under the name of anarthritic rheumatoid disease (Bagratuni, 1956), but its relationship to giant-cell arteritis has not been clearly demonstrated. The cause of the skeletal symptoms is not clear. Although some wasting and weakness is to be expected in elderly patients in the course of a debilitating illness, the patchy distribution of the wasted muscles, the persistence of weakness long after the patient has become ambulant (Case 35), and the fact that many debilitated patients have no skeletal symptoms, make one suspect some other explanation. Muscle wasting might be presumed to be secondary to joint changes, except that it is out of all proportion to the clinical or radiological involvement of the joints. There was no tenderness, fasciculation, reflex change, or sensory impairment, so that degeneration of anterior horn cells or peripheral nerves is also an unlikely explanation. Perhaps the cause most readily suggested is a myositic process similar to that seen in other collagen diseases. Electromyographic and biopsy findings, however, would be expected to show an abnormality, and none could be found in the cases studied, nor was there any evidence of muscular arteritis, although this is known to occur (Finlayson and Robinson, 1955). Whatever the pathological nature of the skeletal lesions may prove to be, they must clearly be recognized and regarded, along with lesions of the cranial or other arteries, as manifestations of the same disease process.

I wish to thank the physicians of St. Thomas's Hospital, London, for access to the patients reported here, and Dr. J. St. C. Elkington and Dr. R. E. Kelly for valuable advice and criticism.

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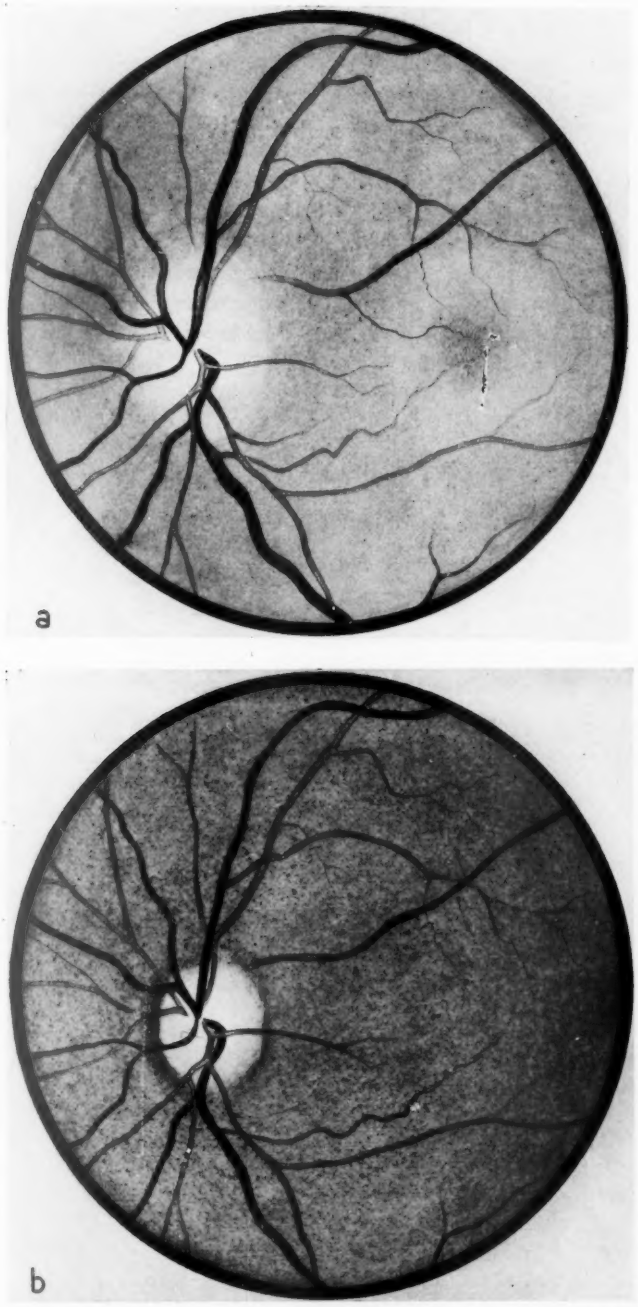
Summary

1. The clinical features of 35 cases of giant-cell arteritis are described, the course of the disease being divided into three stages: the stage of headache, the stage of visual complications, and the stage of systemic complications.

2. Of 16 patients with visual disturbance, five were left completely blind,



Right ocular fundus in a woman aged 63 (Case 2). (*a*) Twelve hours after the onset of visual symptoms, showing retinal and disk oedema and tortuous dilated veins. (*b*) Three weeks later. The retina and vessels are now normal, but the disk shows optic atrophy

five were blind in one eye, five had considerable visual impairment, and one recovered. The mechanism and treatment of ocular complications are discussed. Steroid therapy may prevent spread of the disease to the ophthalmic vessels, but has little effect once symptoms have developed.

3. Various syndromes which may follow or accompany cranial arteritis are described. There may be a general arteritis with skin or visceral lesions, and varieties of peripheral neuritis, or a generalized skeletal disorder with muscle pain and wasting. The cause and the treatment of these syndromes are discussed. Steroid therapy is particularly effective in patients with muscular symptoms, but is considerably less effective in dealing with other complications.

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ANAEMIA IN BRIGHT'S DISEASE[1]

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Anaemia has been recognized as a complication of renal disease since the description by Bright in 1827. The variable oedema which may occur in the disease, however, has led to differing interpretations of the significance of a lowered haemoglobin level, and it was concluded by Steinbeck (1953) that direct measurements of red-cell volume were needed to define the anaemia accurately. The understanding of the mechanism of the anaemia has been complicated by the occasional demonstration of reduced red-cell survival (Emerson, 1948; Finch, Gibson, Peacock, and Fluharty, 1949; Emerson and Burrows, 1949; Chaplin and Mollison, 1953; Joske, McAlister, and Prankerd, 1956; Loge, Lange, and Moore, 1950, 1958). This reduction has been reported most frequently in the terminal stage of uraemia, and it remains uncertain whether or not it is associated with any particular variety of Bright's disease at an earlier stage in its course. The effect of heart failure on the blood volume in Bright's disease is also uncertain. The present investigation was undertaken at the London Hospital to define as precisely as possible the nature and degree of anaemia in a series of patients suffering from Bright's disease. It has been continued in the Department of Medicine in the University of Sheffield by one of the authors. The results in four patients investigated by similar techniques in the Department of Pharmacology and Therapeutics in the University of Sheffield are included.

Methods

Red-cell volume was measured with either radioactive phosphorus-32 or chromium-51, and red-cell survival with chromium-51 by the technique described by Turnbull, Hope, and Verel (1957). By this method the total quantity of labelled cells surviving at any time is estimated directly, and errors due to changes in blood volume or haematocrit level are avoided. The figures obtained by direct measurement of the blood volume were compared with predictions calculated from the patients' bodily measurements (Hicks, Hope, Turnbull, and Verel, 1956). For the purpose of this calculation the patient's weight when free of all clinical oedema was taken. Haemoglobin was measured by the method of Reeve (1944). For haematocrit readings blood was spun for 55 minutes at 15 cm. radius in 10-cm. Wintrobe tubes, and the results corrected for trapped plasma by the factor of Chaplin and Mollison (1952). For reasons to be discussed, plasma volume

[1] Received October 16, 1958.

TABLE I

Clinical and Laboratory Data in 40 Patients with Bright's Disease

Case number	Sex	Age (years)	Diagnosis	Diagnostic criteria (see note 1)	Blood-pressure (mm.Hg)	Papill-oedema	Blood urea (mg./100 ml.)	Predicted normal red-cell volume (ml.)	Measured red-cell volume (ml.)	Venous haemoglobin (g./100 ml.)	Venous haematocrit (%)	Red-cell survival by ^{51}Cr method (see note 2)		
												% remaining in circulation	Days	Result
1	M	26	Acute type 1 nephritis	C	120/80	0	63	1,870	1,880	12·5	36·3	70	10	N
2	F	15	,, ,, ,, ,,	C	170/100	0	30	1,440	925	10·7	31·1	50	25	N
3	M	15	,, ,, ,, ,,	C	130/80	0	48	1,610	1,030	12·9	37·0	..	..	..
4	F	14	,, ,, ,, ,,	C	120/80	0	48	1,600	1,250	8·0	37·5	..	..	..
5	M	34	,, ,, ,, ,,	C	185/110	0	33	2,100	1,390	12·0	33·0	50	25	N
6	M	36	,, ,, ,, ,,	A	180/110	0	400	2,140	900	7·5	23·7	60	18	N
7*a*	M	33	Early type 2 nephritis	C	120/55	0	30	1,820	1,700	13·3	42·5	..	..	..
7*b*		33	,, ,, ,, ,,	C	140/95	0	33	..	1,500	13·7	38·8	..	..	..
8	M	36	,, ,, ,, ,, and Hodgkin's disease	B	200/100	0	120	2,100	1,400	8·9	26·3	50	13	S
9	M	38	Chronic type 1 nephritis	C	230/150	0	75	2,090	1,680	14·6	41·7	65	20	N
10	M	60	,, ,, ,, ,,	C	190/95	0	200	1,900	980	7·6	22·0	50	24	N
11	M	41	,, ,, ,, ,,	A	230/130	?+	120	2,300	1,350	10·4	28·8	50	23	N
12	M		,, ,, ,, ,,		260/140	+	70	2,000	1,440	12·1	38·4	50	24	N
13	M	54	,, ,, ,, ,,	C	210/145	+	93	2,270	..	11·5	32·1	50	26	N
14	M	59	,, ,, ,, ,,	C	290/150	0	60	1,710	1,300	10·7	31·4	55	18	N
15	M	52	,, ,, ,, ,,	A	150/110	0	100	1,700	1,220	10·9	32·8	50	26	N
16	M	50	Chronic type 2 nephritis	A	250/140	0	79	1,750	1,410	11·8	32·8	65	19	N
17	M	66	,, ,, ,, ,,	A	200/120	?+	87	2,400	1,100	9·6	35·4	80	8	N
18*a*	F	25	,, ,, ,, ,,	A	245/150	0	48	1,700	1,230	12·7	36·7	50	24	N
18*b*		26	,, ,, ,, ,, (terminal)		210/130	+	155	..	790	5·5	17·7	50	18	S
19*a*	M	30	Chronic type 2 nephritis. Recent acute haematemesis	C	200/120	0	100	2,500	1,240	8·2	26·0	50	28	N
19*b*		32	Chronic type 2 nephritis		200/120	0	276	..	1,230	6·3	20·0	75	11	N
20	F	25	,, ,, ,, ,,	C	180/120	0	70	1,820	960	7·9	24·0	70	12	N
21	M	59	,, ,, ,, ,,	C	250/130	?+→0	57	1,890	1,670	11·6	35·8	50	22	N
22	F	47	Chronic pyelonephritis	C	245/150	+→0	168	1,350	1,015	9·6	29·9	70	13	N
23	M	25	,, ,,	C	220/130	0	49	..	..	15·9	46·6	50	22	N
24	F	61	,, ,,	C	195/125	0	102	1,560	990	10·0	29·5	70	14	N
25	F	27	,, ,,	C	150/110	0	236	1,580	850	7·2	20·0	75	9	N
26	M	25	Terminal nephritis (type 1)	C	250/140	0	500	1,950	670	5·6	14·9	55	14	S
27	M	27	,, ,, (? type 2)	C	240/150	0	267	1,890	750	6·4	18·6	55	14	S
28	F	22	,, ,, (type 2)	A	215/140	0	111	1,820	865	9·5	27·8	60	16	N

Case number	Sex	Age (years)	Diagnosis	Diagnostic criteria (see note 1)	Blood-pressure (mm.Hg)	Papill-oedema	Blood urea (mg./100 ml.)	Predicted normal red-cell volume (ml.)	Measured red-cell volume (ml.)	Venous haemoglobin (g./100 ml.)	Venous haematocrit (%)	Red-cell survival by ^{51}Cr method (see note 2)		
												% remaining in circulation	Days	Result
29	M	35	Terminal nephritis (? type 1)	C	180/120	0	220	2,080	960	4·6	15·4	50	22	N
30	M	36	,, ,, (type 2)	C	230/120	0	200	2,000	1,040	6·5	19·4	50	23	N
31	M	22	,, ,, (type 1)	C	230/120	+	129	2,050	845	5·7	17·6	65	7	S
32	M	42	,, ,, (type 1)	A	220/120	0	255	..	1,210	7·6	23·4	60	21	N
33	M	25	,, ,, (type 1)	A	210/150	+	264	2,420	1,280	9·6	24·5	50	14	S
34*a*	M	37	Malignant essential hypertension	B	260/175	+	39	1,950	1,450	14·9	40·6	50	18	S
34*b*		38	Benign essential hypertension		215/160	0	41	..	2,120	16·1	47·3	50	28	N
35	F	54	Malignant essential hypertension	A	270/170	+→0	42	2,200	2,320	15·5	47·7	50	23	N
36	M	52	Malignant essential hypertension (controlled)	C	200/130	? 0	48	..	..	14·9	43·2	50	26	N
37	F	28	Benign essential hypertension	C	210/160	0	41	1,350	1,310	13·2	39·2	55	22	N
38	F	68	Diabetic nephrosclerosis	C	180/130	0	48	1,500	1,240	13·0	39·5	50	28	N
39	F	43	Polycystic kidneys	C	175/115	0	41	2,000	665	5·9	19·8	55	25	N
40	F	45	,, ,,	C	210/110	0	63	1,900	1,270	11·2	36·3	50	24	N

1. C = Clinical findings only. B = Clinical findings and renal biopsy. A = Clinical findings and autopsy.

2. For brevity the results of the studies of red-cell survival are reported as the number of days after which the percentage of ^{51}Cr-labelled red cells in the circulation had fallen to 50, or to a higher figure when the study had to be discontinued before this level. Normal limits for these figures, which have been corrected for changes in blood volume, are: 80 per cent.: 5–8 days; 75 per cent.: 7–11 days; 70 per cent.: 9–14 days; 65 per cent.: 12–18 days; 60 per cent.: 15–21 days; 55 per cent.: 18–25 days; 50 per cent.: 22–29 days. N = normal. S = shortened red-cell survival. (See text, and Turnbull, Hope, and Verel, 1957.)

has been determined by calculation from the red-cell volume and venous haematocrit.

Results

The results obtained are shown in Table I. The patients have been grouped by the type and stage of their illness according to the classification of Ellis (1942). Diagnoses have been made on the basis of all the available data, which in 12 cases include renal biopsy or the findings at autopsy. Since, in the later stages of Bright's disease, distinction between the varieties may in many cases be difficult or even impossible except by histological study, a division was simply made between patients in whom renal failure was advancing slowly and those in whom the disease was in its terminal stage. The term malignant hypertension has been used to mean hypertension with papilloedema, whether the elevation in blood-pressure is believed to be 'essential' or due to nephritis or other renal disease.

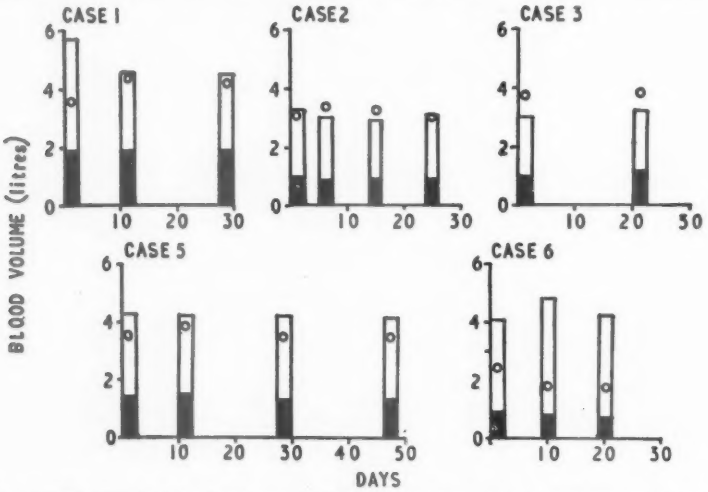

FIG. 1. Changes in blood volume and haematocrit reading in acute type 1 nephritis. The solid rectangles represent the red-cell volumes, the clear rectangles the plasma volumes. The circles show the venous haematocrit level, the figures showing litres being used to indicate the initial figure of the haematocrit reading (e.g. 4 = 40 per cent.).

Acute type 1 nephritis. Six patients were investigated during the initial attack of acute type 1 nephritis. All were oedematous when the first blood-volume measurements were made, and in five the final measurements were made after all clinical oedema had been lost (Table I; Fig. 1). In the first four patients the disease ran a brief course to complete recovery. With the exception of Case 4, the initial measurements were made within two days of the onset of evident oedema. In the first patient the haematocrit reading was 36·3 per cent. on admission, and 44·5 per cent. when the oedema had gone 13 days later, an increase of 18 per cent. of the final value. In normal subjects the daily variation in the venous haematocrit level does not exceed 8 per cent. (Hicks, Hope, Turnbull, and

Verel, 1956), and the change in this patient must therefore reflect some change either in the red-cell or plasma volume, or in the distribution of red cells and plasma in the circulation, the last factor being unlikely. The rise in haematocrit level was not attended by any significant change in red-cell volume, and so presumably indicates a fall in plasma volume. Similar haematocrit changes in acute type 1 nephritis have been reported by Roscoe (1950). In Cases 2 and 3, clinically very similar to Case 1, the red-cell volumes were significantly reduced, and the loss of oedema was attended by insignificant changes in red-cell volume or haematocrit level. In Case 4 the patient was found to have a marked iron-deficiency anaemia (mean corpuscular haemoglobin concentration 21·3 g. per 100 ml. red cells). Treatment with iron resulted in a reticulocyte crisis and a rise in red-cell volume. The findings have not been reported in detail, but the loss of oedema, as in Cases 2 and 3, caused no obvious change in the patient's haematological recovery. These measurements indicate that examination of the peripheral blood in acute type 1 nephritis may show an anaemia which is only apparent, with a normal red-cell volume and increased plasma volume, or may indicate a true anaemia due to a reduced red-cell volume. In Case 5 the disease ran a more protracted course, with persisting renal impairment. In the acute stage the findings resembled those in Cases 2 and 3, the red-cell volume and haematocrit level both being reduced. The slight changes in haematocrit level seen during the period of study accompanied a comparable alteration in red-cell volume, and bore no relation to the fluctuating oedema, which, however, had not completely gone when the final measurements were made. The sixth patient suffered from a severe and rapidly progressive nephritis, which ended fatally after several months. He presented gross oedema, hypertension, and renal failure. The measurements reported here were begun six weeks after the onset of the disease. The red-cell volume fell at a rate suggesting a complete arrest of erythropoiesis (Fig. 1). In the first period of observation there was a corresponding fall in the haematocrit readings, but during the second period they remained constant, although the rate of decrease in the red-cell volume was unchanged. This suggests that the plasma volume was raised during the oedematous phase, as in Case 1. In all these patients the red-cell survival was normal.

The low red-cell volumes observed in Cases 2 and 3 are of considerable interest. In both cases the mean corpuscular haemoglobin concentration was normal, and direct examination of the blood revealed no evidence of iron deficiency. Both volumes were about 500 ml. below normal. Depression of the bone-marrow, which was seen in Cases 5 and 6 at a later stage of acute nephritis, cannot be the full explanation of these findings. The interval between the sore throat preceding the nephritis and the initial measurement of red-cell volume was one month in Case 2 and 14 days in Case 3. With a normal life-span of the red cells, complete arrest of erythropoiesis for this interval would have led to a fall in red-cell volume of about 400 ml. in Case 2 and 200 ml. in Case 3. The additional deficiency in red cells might be accounted for by loss of blood into the urine or elsewhere, or to increased haemolysis. Neither of these patients had haematuria of this severity, and in neither was there indication of any other haemorrhage. Increased

haemolysis might have occurred during the initial infection, but it could not be demonstrated when the patients had reached hospital.

There is no obvious relation between the level of blood urea and anaemia in any of these patients. Thus in Case 1 the red-cell volume was normal and the blood-urea level higher than in Cases 3 and 5, who were anaemic with normal blood urea. The rapid fall in red-cell volume observed in the last patient in this group (Case 6) may have been related to uraemia, but this is unlikely; in other patients an equally high blood-urea level was associated with a much more slowly advancing anaemia.

TABLE II

Spontaneous Recovery from Gastrointestinal Haemorrhage

Serial measurements of red-cell volume and venous haematocrit levels in Case 19a

Date	*Red-cell volume (ml.)*	*Venous haematocrit (%)*	*Rate of rise of red-cell volume (ml. per day)*
10.12.56	1,240	26·0	..
27.12.56	1,670	36·1	25·3
17.1.57	1,910	42·5	11·4

Early type 2 nephritis. Two patients were seen early in the course of type 2 nephritis. In one (Case 7) the blood-volume data were normal. One year later, when he was free of oedema, a slight anaemia was present, with reduced red-cell volume and venous haematocrit level. The blood urea was still normal. The second patient (Case 8) had been given radiotherapy for Hodgkin's disease before the onset of his nephritis. He was found to have a progressive anaemia, with shortening of the red-cell life-span. It was thought that the latter effect was more likely to be due to the coincident reticulosis. He lost his oedema during the course of these observations. In both patients the haematocrit level varied with the red-cell volume, suggesting that any changes in plasma volume occurred in compensation for changes in red-cell volume. Roscoe (1950) and Steinbeck (1953) found similar changes in type 2 nephritis.

Slowly progressive nephritis. Seventeen patients (Cases 9 to 25, excepting 18*b*) were considered to be suffering from slowly progressive nephritis. Nitrogen retention was present in all these patients, and the finding of red cells and casts in the urine indicated that further renal damage was occurring. In spite of these changes, serial measurements of blood urea and creatinine clearance showed only a slow deterioration in the patients' state over months or years. All were reasonably well, and were admitted to hospital for treatment in exacerbations or for regulation of hypotensive therapy. In seven patients (Cases 9 to 15) the original disease was considered to be acute type 1 nephritis, in six (Cases 16 to 21) type 2 nephritis, and in four (Cases 22 to 25) chronic pyelonephritis. In all these patients the venous haematocrit reading was a fair index of the red-cell volume, and no evidence of considerable changes in plasma volume was obtained, except in Case 19*a*, when the patient had been

admitted after an acute haematemesis. Here a normal response to haemorrhage occurred, the red-cell volume rising to a level below the predicted normal for the patient (Table II). The rate at which the red-cell volume increased was within normal limits (Tudhope, 1958). In one other patient, with a red-cell volume of about 60 per cent. of normal, a reticulocyte response of 6 per cent. followed a haemorrhage from a gastric ulcer. Blood transfusion was given, and blood-volume studies were not made.

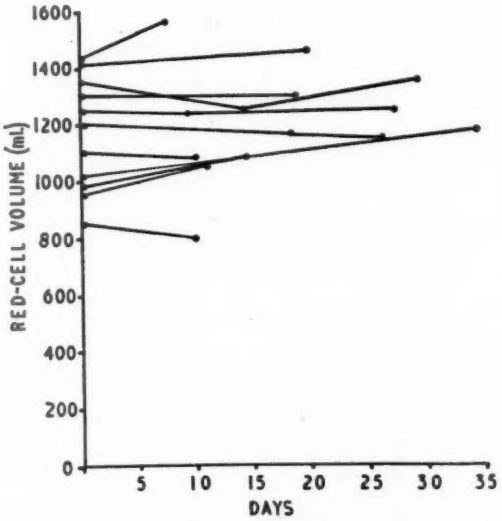

FIG. 2. Red-cell volume changes in chronic nephritis. Little change in volume occurred during the period of observation.

Red-cell survival was normal in all the patients in this group. Serial measurements of red-cell volume (Fig. 2) and venous haematocrit level were made in some of them. These showed that in most cases the red-cell volume was maintained constant from one week to another, although the total volume was depressed. If the red-cell life-span is constant, red-cell volume is an index of the rate of erythropoiesis. In normal subjects the red-cell volume, and hence the rate of erythropoiesis, is maintained at a constant level (Chaplin, 1954). The observations in these patients suggest that, in the stage of nephritis when the degree of renal impairment changes little from week to week, erythropoiesis is depressed by a constant amount in each subject. The relation between blood urea and red-cell volume (and hence erythropoiesis) is shown in Fig. 3, and is less obvious than that found between haemoglobin and urea by Roscoe (1950). All her patients, however, suffered from type 2 nephritis.

Terminal nephritis. Nine patients (Cases 18*b* and 26 to 33) were investigated in the terminal stage of nephritis. All were severely anaemic, and the red-cell volume fell rapidly during the period of observation (Fig. 4). The venous haematocrit level fell with the red-cell volume in most cases, but in one patient

(Case 28) the fall in haematocrit level greatly exceeded the fall in red-cell volume. This haemodilution accompanied a progressive increase in oedema due to heart failure, and is discussed later. In five subjects (Cases 18*b*, 26, 27, 31,

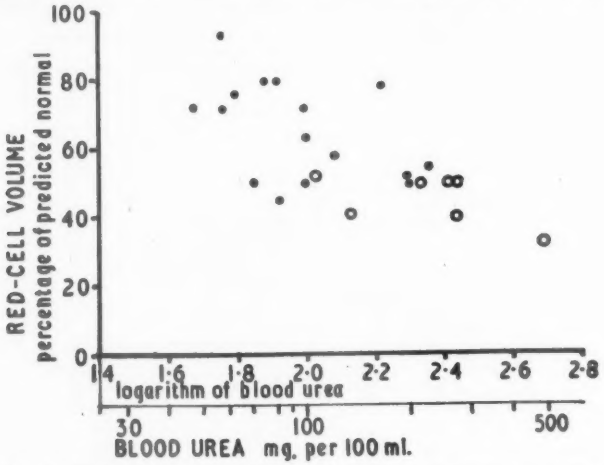

FIG. 3. Red-cell volume related to blood urea in patients with chronic nephritis (dots) and terminal nephritis (circles). Blood urea has been plotted as a logarithm (compare Roscoe, 1950).

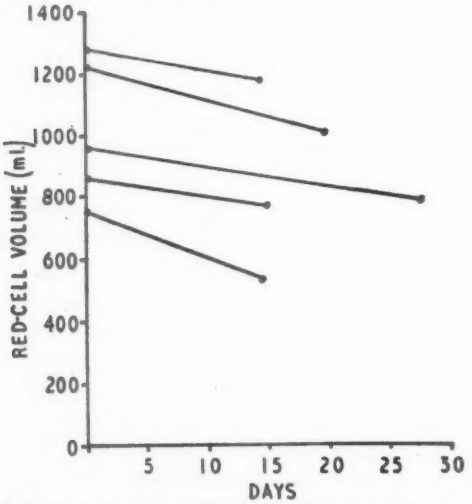

FIG. 4. Red-cell volume changes in terminal nephritis. In all cases the red-cell volume fell during the period of observation.

and 33) the red-cell survival was shorter than normal, but in none of them was the shortening sufficient to account for the decline in red-cell volume, nor was there reticulocytosis or other evidence of increased regeneration of blood. As in the other patients in this group, in whom the cell survival was normal, the

increasing anaemia can be accounted for only by a progressive arrest of erythropoiesis coincident with a rapid increase of blood urea. Three of the patients in whom red-cell survival was shortened (Cases 18*b*, 31, and 33) were the only subjects in this group to have papilloedema, and this condition was little changed by hypotensive therapy. Papilloedema was not found in Cases 26 and 27, which could not be differentiated clinically from the cases in this group showing normal red-cell survival.

TABLE III

Effect of Heart Failure on Venous Haematocrit and Red-Cell Survival Measurements

Case number	*Date*	*Red-cell volume (ml.)*	*Blood volume (ml.)*	*Venous haematocrit (%)*	*Survival of ^{51}Cr-labelled cells*		
					Uncorrected (%)	*Corrected (%)*	*Normal (%)*
18*a*	5.5.56	1,240	3,680	36·7	100	100	100
	14.6.56	1,230	3,710	33·1	68	75	73–83
	2.7.56	1,250	4,200	32·5	40	45	44–52
28	24.1.56	865	3,400	27·8	100	100	100
	9.2.56	775	4,140	20·3	50	61	58–67
29	12.3.56	960	6,570	29·9	100	100	100
	9.4.56	780	6,030	30·4	44	41	41–51

Data of blood volume and ^{51}Cr survival selected to show the effect of heart failure. In two patients (Cases 18*a* and 28) the rising plasma volume produced sufficient dilution of the labelled cells to cause an apparent shortening of red-cell survival. In the third patient (Case 29) the falling plasma volume has concealed a considerable deterioration in the patient's state. In all cases blood volume has been calculated from the red-cell volume and body haematocrit.

Malignant essential hypertension. Three patients with malignant essential hypertension were investigated (Cases 34, 35, and 36). In one patient (Case 34) red-cell survival was estimated twice. During the first estimate he had gross papilloedema, and was moderately anaemic. The red-cell survival was shortened. The observations were repeated one year later, after the fundal changes had subsided as a result of hypotensive therapy, and both the blood picture and the red-cell survival were found to have returned to normal. In the remaining two patients red-cell volume, venous haematocrit level, and red-cell survival were normal. In both these patients papilloedema lessened as a result of therapy during the estimations.

Observations were made in four other patients. In one, with benign essential hypertension (Case 37), the red-cell volume, haematocrit reading, and red-cell survival were normal. Red-cell survival was also normal in one patient with diabetic nephrosclerosis (Case 38) who was mildly anaemic. In two patients with polycystic kidney disease the red-cell volume was reduced, with a compensatory rise in plasma volume. In both these patients the mean corpuscular haemoglobin concentration was at the lower limit of normal, and the red-cell survival was normal. In these two patients the reduction in red-cell volume seemed greater than might be expected from the degree of renal impairment. Their profuse haematuria may have been partly responsible.

The effect of cardiac failure is illustrated by three patients (Table III). Increasing oedema due to heart failure was observed in Case 18*a* during the measurement of red-cell survival. A coincident increase of 510 ml. in the plasma volume caused a fall in the venous haematocrit level from 36·7 per cent. to 32·5 per cent., although the red-cell volume remained constant. In Case 28 the coincidence of a similar increase (830 ml.) in plasma volume and a decline in the red-cell volume from 865 to 775 ml. caused the venous haematocrit level to fall from 27·8 per cent. to 20·3 per cent. In both these patients the rise in blood volume lowered the level of circulating chromium-51 enough to suggest a shortening of red-cell survival. When correction for haemodilution was applied (Turnbull, Hope, and Verel, 1957) the survival values were found to be normal. In Case 29 recovery from heart failure minimized the change in haematocrit levels, and concealed the true extent of the deterioration revealed by the figures for red-cell volume. In this patient the calculated plasma volume fell by 360 ml. in one month. In the same time the red-cell volume fell from 960 ml. to 780 ml., while the venous haematocrit reading showed no significant change. The changes in volume in this case were not enough to invalidate the estimate of red-cell survival.

Discussion

Numerous attempts to define the nature of the anaemia in Bright's disease by plasma-volume measurement have been reported (Steinbeck, 1953; Roscoe, 1950; Cardozo, 1946; Harris and Gibson, 1939; Waterfield, 1930–1; Brown and Rowntree, 1928; Darrow, 1925–6). Differing conclusions were drawn from these observations, the plasma volume in Bright's disease being thought to be unduly high, normal, or reduced. Most direct measurements of plasma volume have been made by determining the space occupied by plasma albumin, Evans blue being most frequently used for this purpose. Recent work has cast doubt on the validity of such measurements in oedematous subjects. Joenike, Schreiner, and Waterhouse (1957) and Verel (1958) made simultaneous measurements with albumin and dextran of high molecular weight. In both investigations it was found that in oedematous subjects the albumin diffused into a larger space than the dextran. The authors concluded that the albumin leaked from the vascular compartment, thus invalidating the measurements. In such circumstances it might seem better to calculate the plasma volume indirectly from the red-cell volume and venous haematocrit. Such calculations are valid in normal subjects (Hicks, Hope, Turnbull, and Verel, 1956; Semple, 1956; Semple, Thomsen, Ball, and Excell, 1956; Verel, 1958), but are liable to error in anaemia, partly because of the relative increase in the difference between arterial and venous haematocrit, and partly because of changes in the distribution of red cells and plasma (Hope and Verel, 1955). It follows that the venous haematocrit level can be used as an index of changes in plasma volume only if neither the red-cell volume nor the distribution of red cells and plasma in the circulation have changed significantly. Provided no sudden change, such as shock or severe haemorrhage,

has occurred, this assumption is probably justified, but in oedematous states there is no reliable means of measuring the plasma volume, and so no way of checking the validity of the indirect estimate.

Valid evidence of anaemia is obtained by comparing the red-cell volume, measured by tagged red cells, with the normal predicted from body measurements, and by this criterion the majority of the patients in the present series were anaemic (Table I). Only one showed definite evidence of iron deficiency. Loge, Lange, and Moore (1958) also found iron deficiency rare in a series of patients suffering from chronic nephritis. In most of our patients anaemia was the result of depressed erythropoiesis, and two patterns may be distinguished. In some patients the arrest of erythropoiesis was almost complete, and rapid falls in red-cell volume were observed. This phenomenon was seen in early type 1 nephritis and in terminal nephritis, and in neither condition was it obviously related to the degree of uraemia. In other patients a moderate or considerable depression of the red-cell volume was observed over long periods. In such patients the anaemia was seen to be related to the degree of uraemia (Fig. 3). An apparent anaemia occurred as a result of fluid retention in acute type 1 nephritis, but was less common than in the series reported by Roscoe (1950). Somewhat similar findings were seen in occasional patients admitted with chronic nephritis and heart failure. It may be that the fluid retention in acute type 1 nephritis is also cardiac in origin, but this is unlikely. In the present state of confusion in our understanding of heart failure no firm opinion seems justified.

Shortening in the life-span of red cells has been reported in acute and chronic Bright's disease (Finch, Gibson, Peacock, and Fluharty, 1949; Emerson and Burrows, 1949; Loge, Lange, and Moore, 1958; Chaplin and Mollison, 1953; Joske, McAlister, and Prankerd, 1956). In all these studies the conventional technique of measuring the level of the identifiable cells in venous blood has been used. It has long been recognized that considerable changes in the total blood volume during the period of study may invalidate such results, but most observations, particularly those made by the Ashby (1919) technique, have continued for some weeks, a period so long that any errors due to change in total volume are evident from the shape of the survival curve. Measurements made on patients suffering from Bright's disease are of necessity often of short duration and, as in Cases 18*a* and 28, the normal method may be demonstrably erroneous. A calculation based upon the packed cell volume of the sample used for the estimation of survival and a simultaneous measurement of the red-cell volume has been applied in the results presented here. This calculation is independent of volume changes (Turnbull, Hope, and Verel, 1957).

Seven patients in the present series were found to have shortened red-cell survival. One (Case 8) suffered in addition from Hodgkin's disease, which may account for the shortening. Discussion will therefore be restricted to the remaining six. Five of these patients (Cases 18*b*, 26, 27, 31, and 33) died shortly after the measurements were made. They were suffering from chronic renal impairment of varied aetiology. In these patients the shortening of red-cell survival was thought to be relatively recent in onset, and in one (Case 18*b*) a

study one year previously had shown a normal red-cell life-span. The sixth patient (Case 34*a*) suffered from malignant essential hypertension at the time when a shortened survival was found. One year later, as a result of treatment with hypotensive drugs, his hypertension was benign in character, and the red-cell survival was normal. In the present series shortening of the red-cell life-span does not appear to be related to any particular variety of Bright's disease. Although five of these six patients were in the terminal phase of their illness, their renal function was no worse than that found in the four other patients in a terminal phase, in whom red-cell survival was normal. The blood urea in the six patients with shortened cell survival ranged between 39 mg. and 267 mg. per 100 ml., and in Case 34*a* renal function was entirely normal. The quantity of blood lost in the urine did not account for the survival figures. It was measured in three patients (Cases 18*b*, 27, and 34*a*), and was insignificant compared with the loss of cells that could be calculated from the blood-volume data. Furthermore, haematuria was much more profuse in the subjects with polycystic kidneys, in whom the cell survival was normal (Cases 39 and 40). No clear relation was apparent between the changes in red-cell volume and the presence or absence of a shortened red-cell life-span. Thus, in the patients who died with short cell-survival times, the red-cell volumes fell during the period of observation, but the rates of fall were not different from those observed in similar patients with a normal red-cell life-span. Moreover, in Case 34*a* the red-cell volume was maintained at a constant, although lowered, level in spite of the shortened life-span. Reports of elevation of the reticulocyte count in nephritic patients with shortened red-cell survival (Chaplin and Mollison, 1953; Kaye, 1958) also suggest that the shortening is independent of the depression of erythropoiesis. Other authors (Joske, McAlister, and Pankerd, 1956; Loge, Lange, and Moore, 1958) have failed to find evidence of an auto-immune mechanism. Our experience is similar, the Coombs test being negative in three of these six patients. Nevertheless, there is considerable evidence from cross-transfusion experiments which indicates that an extracorpuscular factor is responsible for the haemolysis (Sutherland, McCall, Jones, and Muirhead, 1955; Joske, McAlister, and Prankerd, 1956; Loge, Lange, and Moore, 1958; Kaye, 1958; Desforges and Dawson, 1958). It is possible that this 'factor' interferes with intermediary red-cell metabolism (Rees, Scheitlin, Pond, McManus, Guild, and Merrill, 1957).

Consideration of the clinical state of the patients in our series with shortened red-cell life-span reveals a possibly significant association. In the two patients in whom the red-cell survival was found on one occasion to be normal and on another to be shortened, the shortening coincided with the presence of malignant hypertension. Further, of the six patients under consideration, four showed malignant hypertension at the time of the study. Chaplin and Mollison (1953) noted the presence of papilloedema in all six of their cases of 'rapidly progressive renal failure' (terminal nephritis), in five of whom the red-cell life-span was shortened. Against this hypothesis are the observations in four of our patients (Cases 12, 13, 22, and 35) in whom undoubted papilloedema was present at the

beginning of the study, but whose red-cell survival was normal. All these patients, however, responded well to hypotensive therapy, with regression of the eye signs, during the survival measurement, and the 'malignant' process would therefore be arrested.

It has been noted that five of our patients with shortened red-cell survival were in the terminal stage of their illness. Of the 10 patients studied by Loge and his colleagues (1958) all five with shortened cell survival were in the terminal stage. The four patients with shortened cell survival studied by Joske, McAlister, and Prankerd (1956) also had advanced renal failure. In contrast, Kaye (1958) found shortening in five of 10 cases, none of which appear to have been 'terminal'; and Desforges and Dawson (1958) found shortening in 11 out of 14 cases, and stated that there was no correlation between the decreased red-cell survival and the degree of azotaemia. Unfortunately the presence or absence of papilloedema was recorded by none of these authors. Thus the possible association of haemolysis with the malignant phase of hypertension remains a subject for further study. Shortening of the red-cell life-span appears to have occurred less often in our patients than might have been expected from the studies mentioned above. It is probable that this is partly due to differing clinical material, but, in view of the findings of Kaye (1958) and Desforges and Dawson (1958), it is not necessarily due to the inclusion of a greater or lesser number of terminal cases. Another possiblity is that in other series results have been obtained which erroneously suggest shortening of red-cell survival, as in our Cases 18*a* and 28, in which a rise in blood volume diluted the level of circulating chromium-51 sufficiently to suggest increased haemolysis. In patients with Bright's disease changes often occur in red-cell volume and in plasma volume, the latter in association with varying oedema and heart failure. If a valid estimate of red-cell life-span is to be obtained in these circumstances, correction must be made for such changes by repeated measurement of the red-cell volume throughout the survival study.

We have been indebted to Professor Clifford Wilson throughout this investigation for his interest, criticism, and encouragement, and to Lord Evans, Professor Stuart-Harris, and Professor G. M. Wilson for access to patients.

Summary

1. Blood-volume studies have been made in 40 patients suffering from Bright's disease. In most of these patients the red-cell survival has been determined by the use of radioactive chromium-51.

2. In the early stage of acute type 1 nephritis anaemia may be due to an increase in plasma volume, the red-cell volume being normal. More commonly it is due to a considerable fall in red-cell volume, the total blood volume being normal. Serial observations suggest that an arrest of erythropoiesis is a major factor in causing this anaemia, and a rapid fall in red-cell volume may be observed in patients in whom the disease runs a rapid course to death.

3. In two patients with early type 2 nephritis the total blood volume was normal.

4. In slowly progressive nephritis the red-cell volume is usually maintained at a constant level, which is lower than normal. Loss of blood in such patients may be followed by a return to the previous low red-cell volume. The total blood volume is usually normal.

5. In terminal nephritis the red-cell volume may fall rapidly as a result of an arrest or slowing of erythropoiesis.

6. Shortening of the red-cell survival may occur at any time in the disease, although most frequently in the terminal stage. It is often found to be associated with malignant hypertension.

7. Heart failure may produce an apparent anaemia by causing haemodilution.

8. Conventional methods of measuring red-cell survival were invalidated in two patients by changes in total blood volume due to heart failure.

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THE EFFECTS OF THYROTOXICOSIS UPON THE METABOLISM OF CALCIUM, PHOSPHORUS, AND NITROGEN[1]

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The purpose of the present paper is to report the results of balance studies for calcium, phosphorus, and nitrogen in patients with thyrotoxicosis. Estimations of serum calcium, inorganic phosphorus, and alkaline phosphatase were made throughout the course of the disease, and these findings are included. The importance of endocrine influences upon the skeleton is well recognized. The earliest reference to the disordered metabolism of bone in the presence of thyrotoxicosis seems to be that of von Recklinghausen (1891). Necropsy of a woman aged 23 years, who died of thyrotoxicosis, revealed prominent vascular striae in the long bones, which split on section 'like rotten wood'. Similar references to the effects of thyrotoxicosis upon the skeleton were made by Hamig (1897), Hoennicke (1905), Tolot and Sarvonat (1906), and von Jaksch and Rotky (1908–9). Thyrotoxicosis is a disease which is recognized in its early stages, and responds to treatment. For this reason overt bone disease is now rarely found with it, but there are several early references to this association. Latzko (1901) found that the condition was sufficient to cause bone pain. Spontaneous fractures were reported by Gottlieb and Schachter-Nancy (1937) and by Crotti (1938). Bartels and Haggart (1938) reported compression fractures of the vertebrae in two patients with hyperthyroidism. Our studies show that the metabolic disturbance is both widespread and severe, and suggest that bone disease would develop if thyrotoxicosis were not treated. Interest in this subject was aroused after antithyroid drugs produced improvement in the calcium balance in a patient with idiopathic osteoporosis. The precise mechanism by which the thyroid gland influences bone metabolism is unknown, but the pattern of the disturbance is remarkably constant, and forms a basis from which to commence further investigation. Nine patients, three men and six women, were selected for study (Table I). Their ages ranged from 16 to 57 years. They were not confined to bed, but were encouraged to be as active as possible, and to take walks in the hospital grounds.

[1] Received October 29, 1958.

Diagnosis

Brief clinical details appear in the Appendix. From a clinical point of view the diagnosis of thyrotoxicosis was not in doubt. The basal metabolic rate was determined in every case by the same operator. The results of a preliminary test were excluded, since initial estimations often give high results owing to apprehension engendered by the sight of the apparatus. The results appearing in the Table are the mean of at least two separate readings. With one exception the diagnosis was confirmed by radioactive iodine studies.

TABLE I

Case number	*Sex*	*Occupation*	*Age (years)*	*Duration of symptoms*	*Basal metabolic rate*	*'T'*	*Thyroid clearance (ml./min.)*
1	M	Joiner	38	4 months	+95	..	638
2	F	Housewife	34	1 year	+37	149	505
3	M	Van driver	25	3 years	+67	98	810
4	F	Clerk	29	3 months	+78	163	466
5	F	Schoolgirl	16	1 year	+51	98	683
6	M	Builder	51	2 years	+51	560	698
7	F	Housewife	44	4 months	+32	..	..
8	F	Housewife	57	3 months	+43	41	124
9	F	Housewife	44	3 months	+73	108	104
		Normal values			+10	3–13	10–80

$'T' = \frac{a \times 100}{b \times c}$; a = % radioiodine in 0–8 hrs. specimen of urine. b = % radioiodine in 8–24 hrs. specimen of urine. c = % radioiodine in 0–48 hrs. specimen of urine.

Methods

The patients were studied in the metabolic unit of the Institute of Orthopaedics, and full balance studies were undertaken for calcium, phosphorus, and nitrogen, with frequent estimations of faecal fat. Blood for analysis was taken at a constant time of day. Collection periods were of six days. During a preliminary trial period, attempts were made to construct a diet as similar as possible to that taken by the patient before admission. It was felt that much false information results from the use of abnormal diets in the performance of balance studies. Three menus were prepared, and given in rotation in order to minimize boredom. These diets were equivalent in calcium and phosphorus content. A duplicate diet for a three-day period was collected, and analysed after emulsification in a Waring blendor. These values were checked against theoretical values from food analysis tables, and are used in the construction of the metabolic charts. Analyses were repeated at monthly intervals, or whenever the diet was changed. Faeces were collected in six-day periods separated by carmine markers; analysis followed emulsification in a Waring blendor. All homogenates were weighed, and weighed portions ashed for calcium and phosphorus estimation. Fat and nitrogen were estimated in weighed samples of wet homogenate. Urine was preserved in 1 per cent. hydrochloric acid, and a measured sample taken for analysis after thorough mixing. Calcium in food, faeces, and urine, was estimated by a flame-photometer method developed by Walker and Woollen (in publication). Phosphorus was estimated by the method

of Briggs (1922); nitrogen by the method of Koch and McMeekin (1924); and faecal fat by a modification of King's method (1947). Calcium in serum was estimated by the method of Clark and Collip (1925); serum inorganic phosphorus and alkaline phosphatase by King's methods (1947).

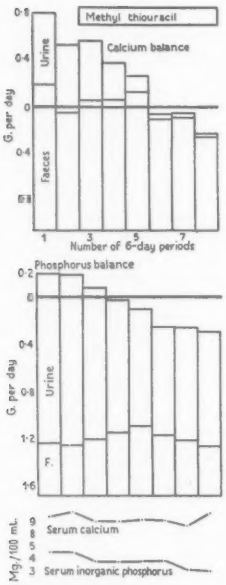
Metabolic charts are constructed according to the method of Albright and Reifenstein (1948). Separate charts are constructed for calcium, phosphorus,

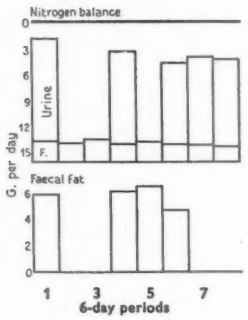
TABLE II

Mean Values for Serum Calcium, Phosphorus, and Alkaline Phosphatase

	Calcium (mg./100 ml.)	*Inorganic phosphorus (mg./100 ml.)*	*Alkaline phosphatase (King-Armstrong units/100 ml.)*
Patients before treatment	9·19	4·25	12·3
Patients after treatment	9·11	3·74	16·2
	0·08	0·51	3·9
	Not significant $P > 0·6$	Significant reduction $P < 0·02$	Significant increase $P < 0·01$
Normal controls	9·30	3·5	6·5
Patients before treatment	9·19	4·25	12·3
	0·11	0·75	5·8
	Not significant $P > 0·7$	Significant increase $P < 0·01$	Significant increase $P < 0·01$
Normal controls	9·30	3·5	6·5
Patients after treatment	9·11	3·74	16·2
	0·19	0·24	9·7
	Not significant	Not significant $P > 0·1$	Significant increase

and nitrogen; estimations of faecal fat are plotted in the relative six-day period. The distance below the zero line to the base-line represents the intake, and upon this base-line, to the same scale, are plotted the faecal and urinary excretions, the latter above the former. If output exceeds intake (negative balance) the excess appears as an area above the zero line. An excess of intake over output is represented by a gap below the zero line above the representation of the faecal and urinary excretion. The values plotted are average daily values, obtained by analysis of a six-day collection of urine or faeces, or of a three-day collection of food homogenate. Each block represents the state of affairs during a period of six days. A gap indicates that the periods were not consecutive. In order to conserve space, precise numerical data from which the charts are constructed are not included.





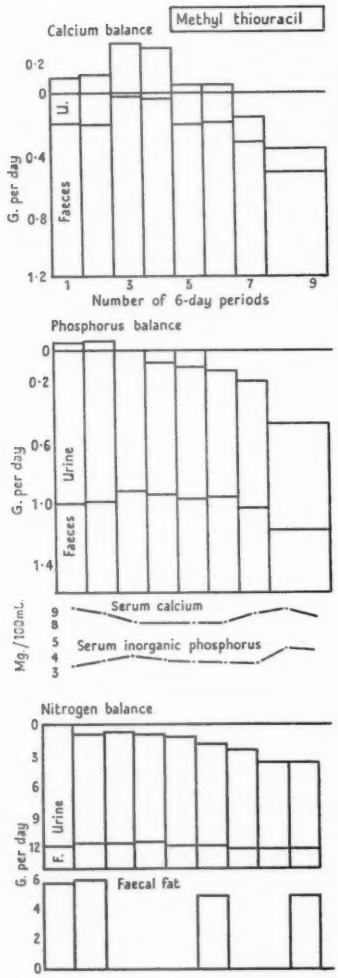
CASE 1. A man aged 38 years.

Periods 1 to 2. Balances for calcium and phosphorus were strongly negative. Faecal calcium exceeded intake, and urinary calcium was in excess of 500 mg. per day. Nitrogen balance was positive.

Periods 3 to 8. Methyl thiouracil given orally (600 mg., reduced to 150 mg., per day) produced a rapid reduction in urinary calcium, and a later reduction in faecal calcium, to render the calcium balance strongly positive. Parallel changes occurred in the phosphorus balance. The positive nitrogen balance tended to increase. Faecal fat exceeded the accepted normal of 5 g. per day, except for the final reading, which was within normal limits.

Serum Analyses

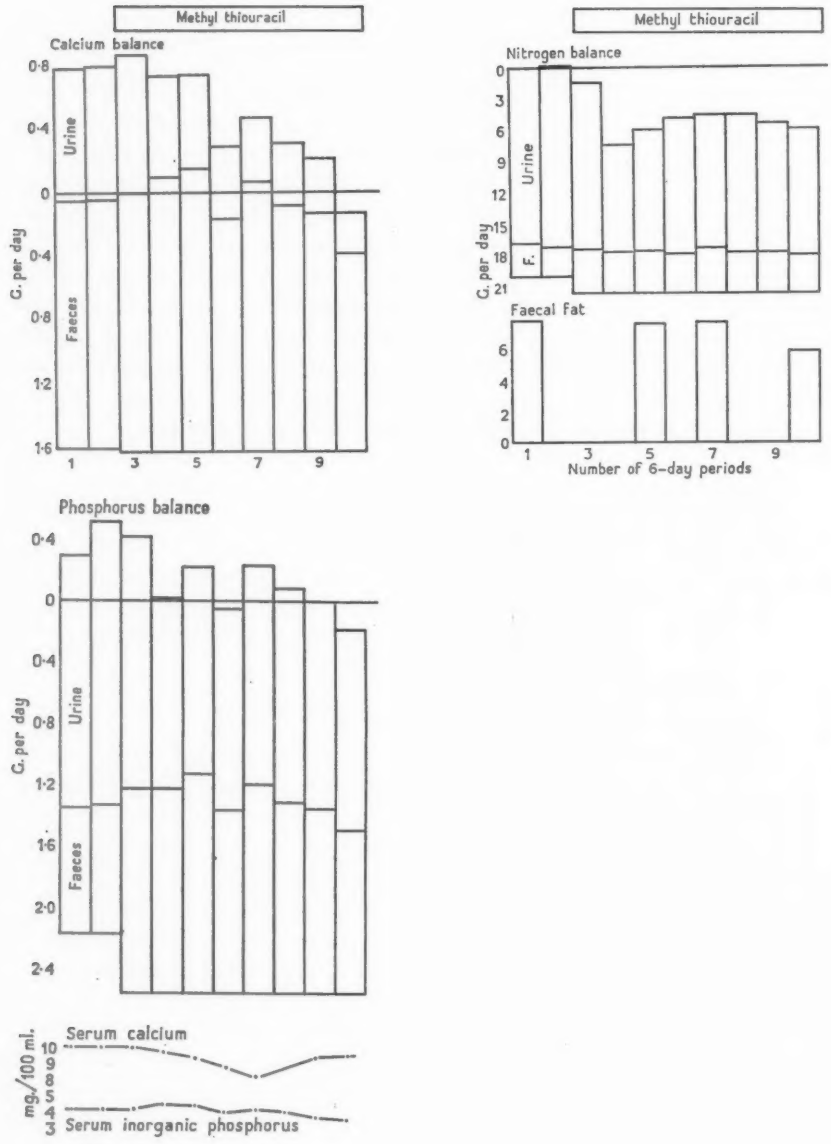
In order to demonstrate trends, the results of serum-calcium and serum-phosphorus estimations are plotted upon the metabolic charts in the period to which they refer. In addition, arithmetic means were calculated for each patient for the periods before and after treatment of the thyrotoxicosis. Those estimations which might have been influenced by other factors, such as calciferol, or the attack of cholecystitis in one case, were disregarded. Normal values for serum calcium were obtained from a series of 55 normal subjects, aged between 20 and 50 years, investigated at the laboratory of the Institute. This was because it is recognized that results of serum calcium estimations vary slightly between different laboratories, possibly because of minor variations of method. Normal values for serum inorganic phosphorus and alkaline phosphatase were as given by King and Wootton (1956). The means and normal values were subjected to statistical analysis, and the results are summarized in Table II.



CASE 2. A woman aged 34 years.

Periods 1 to 4. The patient was in negative balance for calcium, and just in balance for phosphorus. The nitrogen balance was positive. Faecal fat was slightly above normal.

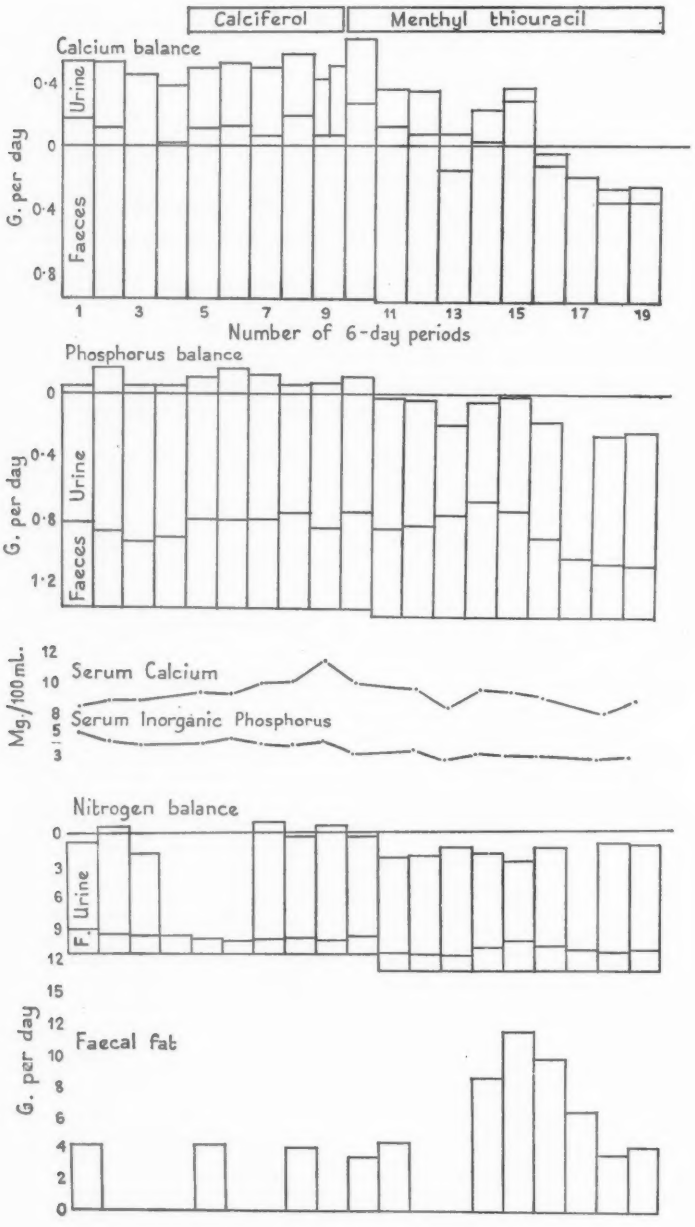
Periods 5 to 9. Methyl thiouracil 600 mg. daily, given orally (reduced to 400 mg. in period 9), produced a reduction in both urinary and faecal calcium, and a positive balance. Similar changes occurred in the phosphorus balance. The nitrogen balance became more definitely positive.


Methyl thiouracil
Calcium balance
Urine
Faeces
G. per day
0·8
0·4
0
0·4
0·8
1·2
1·6
1
3
5
7
9
Methyl thiouracil
Nitrogen balance
Urine
F.
G. per day
0
3
6
9
12
15
18
21
Faecal Fat
6
4
2
0
1
3
5
7
9
Number of 6-day periods
Phosphorus balance
Urine
Faeces
G. per day
0·4
0
0·4
0·8
1·2
1·6
2·0
2·4
mg./100 ml.
Serum calcium
10
9
8
5
4
3
Serum inorganic phosphorus

CASE 3. A man aged 25 years.

Periods 1 and 2. The level of faecal calcium approached the intake; urinary calcium was 800 mg. Phosphorus balance was negative. The patient was in balance for nitrogen.

Periods 3 to 10. The patient received methyl thiouracil, 300 mg. daily. A rapid reduction in urinary calcium was followed by a slower reduction in faecal calcium, to produce a positive balance in period 10. Similar changes occurred in the phosphorus balance. Faecal fat diminished, but remained in excess of the accepted normal.


Calciferol
Menthyl thiouracil
Calcium balance
Urine
Faeces
G. per day
0·4
0
0·4
0·8
1
3
5
7
9
11
13
15
17
19
Number of 6-day periods
Phosphorus balance
0
0·4
0·8
1·2
Serum Calcium
Serum Inorganic Phosphorus
Mg./100 mL.
12
10
8
5
3
Nitrogen balance
F.
0
3
6
9
12
15
Faecal fat
12
10
8
6
4
2
0

CASE 4. A woman aged 29 years.

Periods 1 to 4. Faecal calcium was in excess of the dietary intake, and urinary calcium 400 mg. Phosphorus balance was negative. Faecal fat was within normal limits. Nitrogen balance was positive.

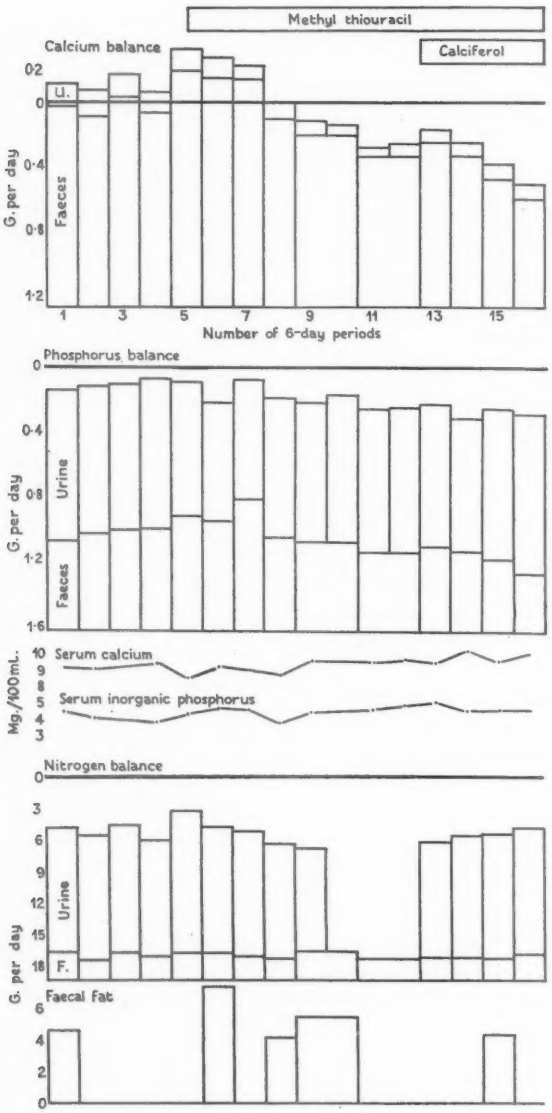
Periods 5 to 8. Calciferol 0·25 mg. daily, given orally, was without effect upon the balance.

Period 9. A large dose of calciferol (2·5 mg. daily, orally) was also without effect.

Periods 10 to 13. Methyl thiouracil (600 mg. daily) produced a prompt reduction in both urinary and faecal calcium, so that the balance became much less negative.

Periods 14 to 15. At this stage the patient developed acute cholecystitis. There was a striking increase in faecal fat, and calcium in the faeces again exceeded intake.

Periods 16 to 19. With the passing of the attack there was resumed improvement, and the calcium balance became positive. The phosphorus balance also became positive, and there was a reduction in faecal fat to normal levels.

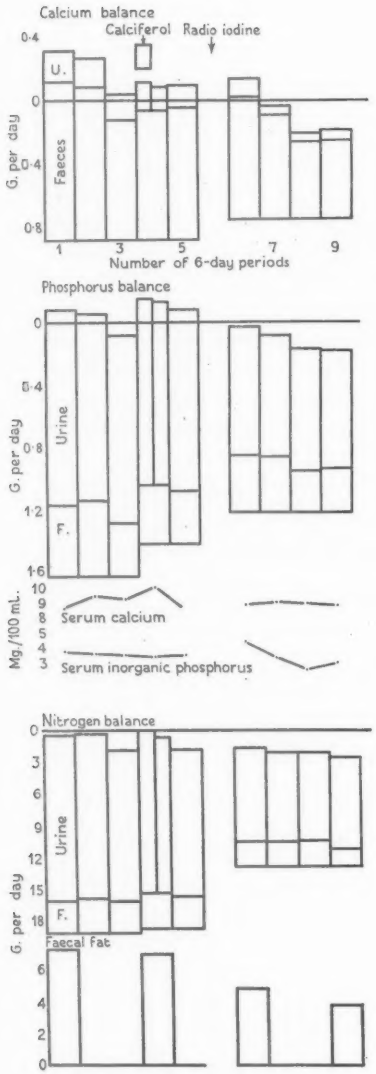

Methyl thiouracil
Calciferol
Calcium balance
0·2
0
0·4
0·8
1·2
U.
Faeces
G. per day
1
3
5
7
9
11
13
15
Number of 6-day periods
Phosphorus balance
0
0·4
0·8
1·2
1·6
Urine
Faeces
G. per day
Serum calcium
Serum inorganic phosphorus
Mg./100 mL.
10
9
8
5
4
3
Nitrogen balance
0
3
6
9
12
15
18
Urine
F.
G. per day
Faecal fat
6
4
2
0

CASE 5. Female patient aged 16 years.

Periods 1 to 4. There was a negative calcium balance as the result of a high level of faecal calcium and probably normal urinary calcium. The average for these four periods was 150 mg. Knapp (1947) quoted 178 mg. per day as an average for normal girls of this age. The nitrogen balance was positive.

Periods 5 to 12. Methyl thiouracil was given, 600 mg. daily, reduced to 200 mg. daily. There was an initial increase in faecal calcium, followed by a steady decrease. Urinary calcium diminished to a level consistently below 100 mg. per day, and a strongly positive calcium balance resulted. The positive phosphorus balance increased slightly.

Periods 13 to 16. Calciferol, 0·25 mg. daily, was given orally. The progressive diminution in faecal calcium continued, and it is impossible to decide whether any further improvement resulted from the calciferol.

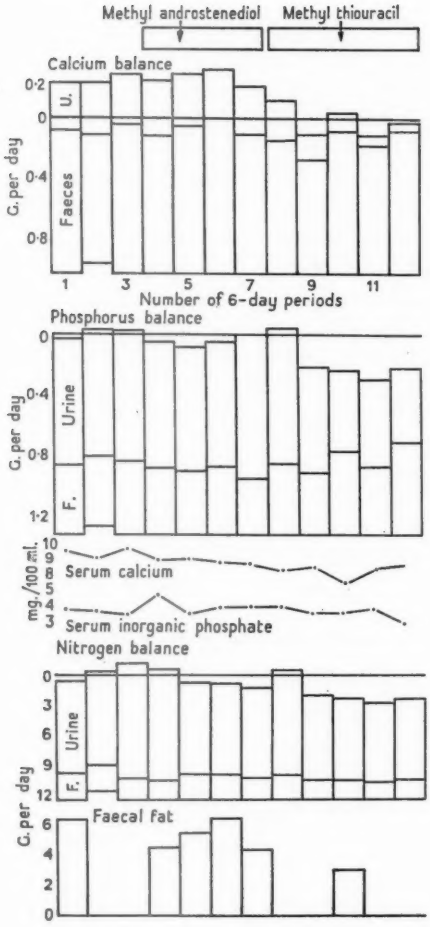


CASE 6. A man aged 51 years.

Periods 1 to 3. Calcium and phosphorus balances were negative. The patient was in balance for nitrogen. The level of faecal fat was high.

Periods 4 to 5. Calciferol, 2·5 mg. given parenterally on each of the first three days of period 4, was without effect upon the balance. Balance studies were discontinued while the patient received radioactive iodine therapy at another hospital.

Periods 6 to 9. Balance studies were recommenced 10 days after therapy, and 14 days after completing period 5. There was a gradual reduction in both faecal and urinary calcium, producing a strongly positive calcium balance. The phosphorus balance became positive, and the nitrogen balance more definitely so. The two faecal fat estimations in this period gave normal results.

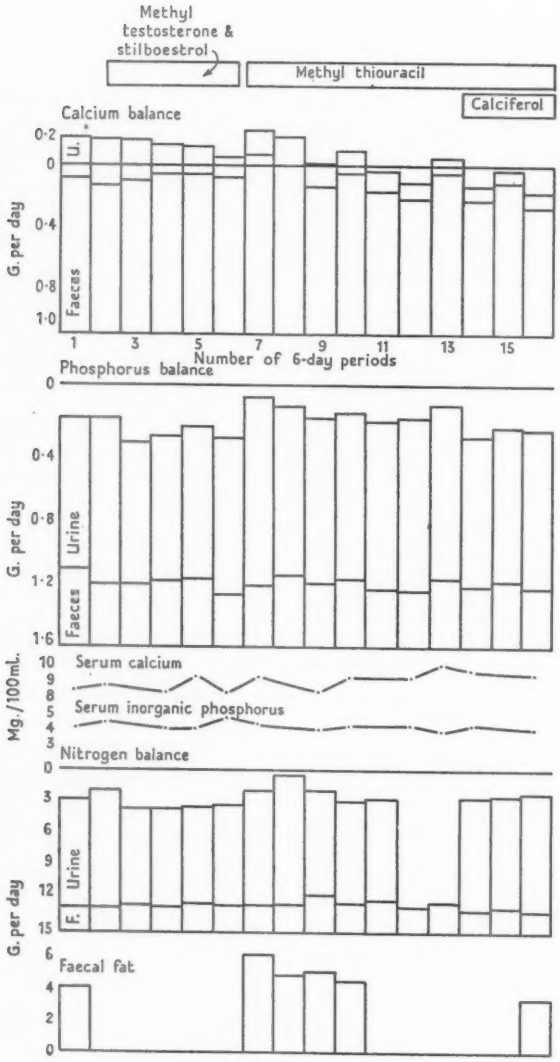


CASE 7. A woman aged 44 years (pre-menopausal).

Periods 1 to 3. There was a negative calcium balance, with zero phosphorus and nitrogen balances.

Periods 4 to 7. Methyl androstenediol, 90 mg. daily, had the desired effect of rendering the nitrogen balance definitely positive. There was no secondary effect upon the calcium or phosphorus balances.

Periods 8 to 12. Methyl thiouracil, 600 mg. daily, reduced to 300 mg. daily, produced a marked reduction in urinary calcium and a less definite reduction in faecal calcium, so that the balance became positive. Similar changes occurred in the phosphorus balance. The nitrogen balance became more positive, and faecal fat decreased to 3 g. per day.


Methyl testosterone & stilboestrol
Methyl thiouracil
Calciferol
Calcium balance
G. per day
U.
Faeces
0·2
0
0·4
0·8
1·0
1
3
5
7
9
11
13
15
Number of 6-day periods
Phosphorus balance
Urine
Faeces
1·2
1·6
Mg./100mL.
Serum calcium
Serum inorganic phosphorus
10
9
8
5
4
3
Nitrogen balance
F.
6
12
15
Faecal fat
2

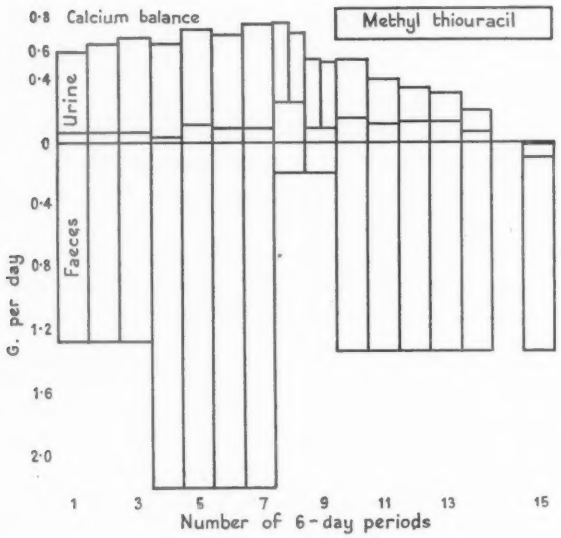
CASE 8. A woman aged 57 years (post-menopausal).

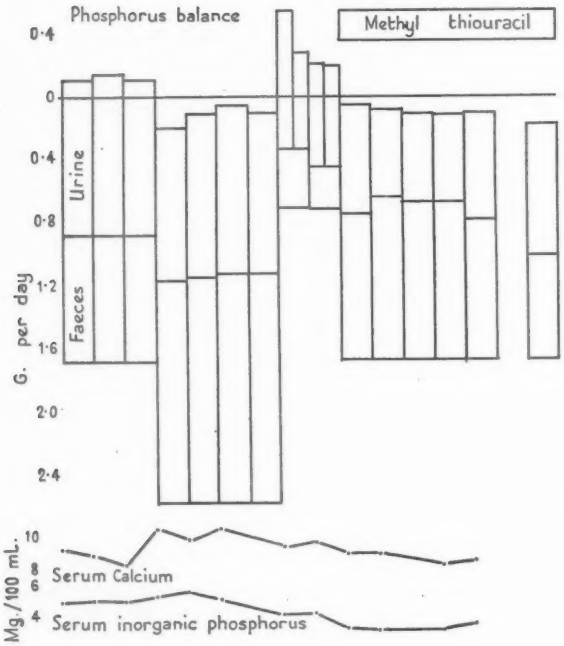
Periods 1 to 2. There was a negative calcium balance, with positive balances for phosphorus and nitrogen.

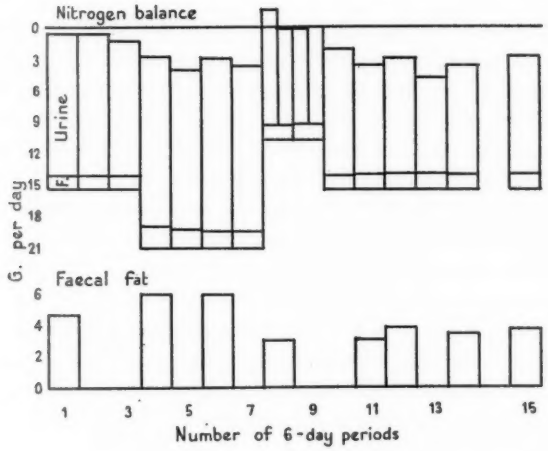
Periods 3 to 6. Methyl testosterone, 10 mg. linguettes, and stilboestrol 1 mg., were given daily. The positive nitrogen balance was slightly increased. Urinary calcium decreased, but faecal calcium was unchanged.

Periods 7 to 13. Methyl thiouracil, 600 mg. daily, produced a reduction in both urinary and faecal calcium, so that the balance became positive. There appeared to be no marked effect upon the phosphorus or nitrogen balances.

Periods 14 to 16. Methyl thiouracil, 200 mg. per day, with 0·25 mg. calciferol, was given orally. The positive calcium balance continued, and the calciferol was without definite effect.


Calcium balance
Methyl thiouracil
Urine
Faeces
G. per day
0·8
0·6
0·4
0
0·4
0·8
1·2
1·6
2·0
1
3
5
7
9
11
13
15
Number of 6-day periods


Phosphorus balance
Methyl thiouracil
Urine
Faeces
G. per day
0·4
0
0·4
0·8
1·2
1·6
2·0
2·4
Mg./100 mL.
10
8
6
4
Serum Calcium
Serum inorganic phosphorus



CASE 9. A woman aged 44 years.

Periods 1 to 3. Faecal calcium exceeded intake, and urinary calcium was more than 500 mg. per day. Nitrogen balance was slightly positive, and phosphorus balance slightly negative. The initial faecal fat estimation gave a normal result.

Periods 4 to 7 show the effect of a high calcium intake (2·2 g. per day). The calcium balance was unaltered, the phosphorus balance slightly positive, and faecal fat increased.

Periods 8 to 9 show the effect of a low calcium intake (0·2 g. per day). The pattern of calcium balance was unaltered, the phosphorus balance became negative, and faecal fat returned to normal.

Periods 10 to 14. Methyl thiouracil, 600 mg. per day, was given orally. There was a gradual reduction in urinary calcium and a delayed reduction in faecal calcium, so that the negative balance was much reduced.

Period 15. The patient was readmitted three weeks after period 14; she spent the interval at home on a normal diet, taking oral methyl thiouracil 100 mg. daily. The calcium balance was positive.

Summary of Findings

A. *Before treatment*

1. All the patients were in negative balance for calcium. The daily loss ranged between 125 and 800 mg. In four cases the daily loss exceeded 500 mg.

2. The rate of urinary calcium excretion was high. In seven of the nine cases it exceeded 250 mg. per day.

3. The rate of faecal calcium excretion was high. In five cases it approached the intake, and in the remaining four cases it exceeded the dietary intake.

4. Faecal fat was increased. Values in excess of the accepted normal of 5 g. per day for an average mixed diet were recorded in all but one case.

5. The phosphorus balance showed no constant pattern. Five patients were in negative balance, two were just in balance, and two in positive balance.

6. The nitrogen balance was positive in seven cases.

7. Serum calcium showed no significant difference from values for normal subjects estimated by a similar method.

8. Serum inorganic phosphorus was significantly increased above normal values.

9. Serum alkaline phosphatase was significantly increased above normal values.

10. Bone biopsies were performed in every case, and no evidence of excessive bone destruction or osteomalacia was found. The histological appearances of osteoporosis (thin trabeculae) were present in six cases. The three cases without evidence of osteoporosis were all of short duration. (Cases 1, 7, and 9; Table I).

11. Anabolic steroids given to two patients rendered the nitrogen balance positive, but were without secondary effect upon the calcium balance.

12. Oral calciferol in varying dosage had no apparent effect upon the abnormal balances. Parenteral calciferol in one patient was equally without effect.

13. In one patient the calcium intake was varied, but this was without effect upon the negative balance.

B. *After treatment*

1. In every case the calcium balance, having previously been negative, was converted to a positive state. This change occurred with methyl thiouracil (eight cases) and with radioactive iodine (one case).

2. In every case a marked reduction in urinary calcium occurred. This change was usually the first to be seen, and made itself apparent by the second or third six-day period after the commencement of treatment. In six patients the values were below 100 mg. per day at the time of discharge from hospital. Random estimations of the calcium content of 24-hour collections of urine, made since the patients have left hospital, have shown that the decreased urinary calcium excretion has persisted.

3. In every case a definite reduction in faecal calcium occurred. This change was slight in one case (No. 7) but marked in the remainder. It was later in making its appearance than changes in the urinary calcium, and usually became apparent after three six-day periods.

4. Faecal fat tended to decrease.

5. All patients had positive phosphorus balances on completion of treatment in hospital. Changes were most striking in those cases in which alterations in the calcium balance were most marked. Those balances which were positive before treatment became more definitely so.

6. The two patients with a negative or zero balance for nitrogen showed a very positive balance after treatment. All the remainder exhibited an increased positive balance.

7. Serum calcium was unchanged.

8. Serum inorganic phosphorus was significantly reduced, and showed no significant variation from normal values at the termination of treatment. The results of subsequent estimations have remained within normal limits.

9. Serum alkaline phosphatase was significantly greater than before treatment. The levels before treatment were above normal, so that the effect of treatment was to raise these levels still further above normal.

Discussion

The above findings demonstrate that the changes in the metabolism of calcium and phosphorus produced by thyrotoxicosis are both widespread and profound. These changes are not widely recognized, because bone pain and spontaneous fractures are very late manifestations of a disease which is soon recognized and treated. In addition, radiography, which is a most important tool in the study of bone disease, is a relatively insensitive indicator of osteoporosis. A large proportion of the calcium of bone needs to be removed before there is indisputable evidence of osteoporosis. Only one patient excreted less than 150 mg. of calcium per day in the urine before treatment, and it may be significant that this was the only patient in whom active skeletal growth was occurring. Perhaps the skeleton is able to compete for the available mineral salts and mitigate the effects of thyrotoxicosis. A plea is made for the possible diagnostic value of the estimation of calcium in a 24-hour specimen of urine in thyrotoxicosis. A low or normal value in an adult should throw doubt upon the diagnosis.

The phosphorus balance was less constant in pattern than the calcium balance. Phosphorus shares in many metabolic processes and, unlike calcium, is not dominated by the metabolism of the skeleton. It is probably for this reason that the characteristics of the balance for phosphorus are less definite. After treatment the phosphorus balance had become positive in every case, and in those cases in which it had been positive before treatment it became more definitely so afterwards. In those cases in which changes in the calcium balance were most marked the phosphorus balance was most altered. In seven cases the nitrogen balance was positive in spite of loss of weight and increased metabolic rate. This fact proves that the body is able to retain nitrogen selectively and meet a negative energy balance by metabolizing fat and carbohydrate. No alteration was detected in serum calcium at any time. The increase in serum

inorganic phosphorus was unexpected, and invites comparison with similar increases that occur in post-menopausal and senile osteoporosis, and in the period of active bone growth in children. Further diagnostic help is suggested by this constant finding. Increased serum inorganic phosphorus in a case of suspected thyrotoxicosis would provide support for the diagnosis.

An increased dietary intake of fat can cause an increment in faecal fat (Wollaeger, Comfort, and Osterberg, 1947), so that the accepted normal value of 5 g. per day may be exceeded (Frazer, 1955). Our patients were receiving normal mixed diets, yet faecal fat usually exceeded normal levels. The reason for this is obscure, but it is probably related to the excess of calcium in the gut. This view is supported by the increase of faecal fat that was associated with the high calcium diet in one patient (Case 9). What other factors influence faecal fat are unknown, but it is obvious that the highest values for faecal calcium are not directly associated with the highest values for faecal fat. It was most interesting to continue the balance study in the patient who developed cholecystitis. This episode produced a marked increase in faecal fat and calcium, and temporarily arrested improvement in the balance.

There has been very little work which is strictly comparable with our findings, since most other balance studies have been conducted with low-calcium diets. In addition, the periods of study seem to have been short, and without adequate preliminary equilibration. Short collection periods of three or four days have been preferred. The earliest study was that of Aub, Bauer, Heath, and Ropes (1929), who reported increased excretion of calcium in the urine and faeces in thyrotoxicosis. They also found serum calcium to be normal. Hansman and Wilson (1934), Hansman and Carr-Fraser (1938), Puppel and Curtis (1936), and Puppel, Gross, McCormick, and Herdle (1945) have all confirmed the increased excretion of calcium in the urine and faeces, with the production of a negative balance. Serum calcium was found to be normal. Laake (1955) reported a raised level of urinary calcium, and normal serum calcium and inorganic phosphorus; the alkaline phosphatase level was raised in one patient. Krane, Brownell, Stanbury, and Corrigan (1956) found a negative balance for calcium in each of four patients with thyrotoxicosis; serum calcium was normal and alkaline phosphatase increased in one patient. Robertson (1942) dissented, in that he found increased excretion of calcium in the urine only. He reported a low level of serum calcium, with a secondary reduction in inorganic phosphorus. This result has not been confirmed by other workers, but there have been references to an increase of serum calcium in thyrotoxicosis (Miller and Evans, 1942; Stanley and Fazekas, 1949).

The results of radiography, the fact that serum calcium and phosphorus were not diminished, and the results of bone biopsy, lead to the belief that the bone disease of thyrotoxicosis takes the form of an osteoporosis. It is impossible to say that in the absence of treatment areas of osteomalacia or osteoclasis would not occur. What is the cause of the disturbance caused by thyrotoxicosis? A direct solvent effect of thyroxine upon the bone surface has been suggested. The mode in which this is brought about is unknown, and the theory must

remain speculative. Loss of protein matrix, with secondary loss of calcium, has been suggested by Kinsell, Hertz, and Reifenstein (1944), Laake (1955), and Albright and Reifenstein (1948). The fact that seven of the patients in the present series had positive nitrogen balances indicates that any protein loss would have to be selective, involving the bone tissues while nitrogen was being stored elsewhere. To test the theory further, methyl androstenediol, which is known to have anabolic properties, was given to one patient (Case 7). The nitrogen balance became definitely positive, but there was no secondary effect upon the calcium balance. Another patient (Case 8), a post-menopausal woman, received stilboestrol and testosterone. The nitrogen balance, which was already positive, became more definitely so. There was a slight reduction in urinary calcium, but no effect upon the faecal calcium. The balance remained negative. The post-menopausal state may have contributed to the patient's negative balance; the effect of stilboestrol and testosterone was similar to that seen in other patients in this age group.

The high level of faecal calcium suggested lack of vitamin D. One patient (Case 4) received oral calciferol (0·25 mg. daily), without any effect upon the balance. A large oral dose (2·5 mg. daily) was equally without effect. Another patient (Case 5) received calciferol orally after treatment had started, and this appeared to be without additional effect. The possibility that oral calciferol was not being absorbed led to parenteral administration in another patient (Case 6). Three daily doses of 2·5 mg. were without effect upon the balance. In retrospect, the fact that high dosage was almost entirely without effect in two patients should not escape notice. There was only one instance of increased serum calcium (Case 4). A relative increase in urinary calcium and a decrease in faecal calcium, the so-called partition effect, might have been expected. The fact that this did not occur indicates that some degree of vitamin-D resistance is a feature of thyrotoxicosis, and warrants further investigation. The possibility of a primary disturbance in the gut was considered, since intestinal hurry is a feature of thyrotoxicosis and the raised level of faecal fat is suggestive. It is difficult, on this basis, to explain the high urinary calcium excretion, and the fact that faecal calcium often exceeds intake. The calcium in the gut consists of unabsorbed dietary calcium (exogenous) and unabsorbed calcium from the digestive juices (endogenous). Direct measurement of endogenous or total digestive-juice calcium is impracticable in human subjects, but approximations have been made by using radioactive calcium isotopes (Blau, Spence, Swernov, Greenberg, and Laszlo, 1957). Another approximation is possible by estimating faecal calcium on the lowest possible intake of calcium. The resultant value represents the difference between total digestive-juice calcium and absorbed calcium, since exogenous calcium is virtually absent. If this value is low it is certain that absorption is efficient, and it is reasonable to assume that total digestive-juice calcium is not greatly increased or, at least, not increased to an extent sufficient to overwhelm the absorptive capacity of the intestine. The measurement was made in one patient (Case 9). With an intake of 0·2 g. per day, faecal calcium varied between 0·3 and 0·5 g. per day. The balance remained

remarkably constant. The values agree very closely with those obtained by Nicolaysen, Eeg-Larsen, and Malm (1953) using a similar method. It appears that increased endogenous calcium is not a factor of importance in the causation of the negative calcium balance in thyrotoxicosis. This is confirmed by the fact that faecal calcium is so strongly influenced by dietary calcium, as in Case 9.

It is probable that the smallest degree of under-saturation of the plasma would lead to mobilization of calcium at the bone surfaces. For this reason the effect of a high calcium intake was studied. It was thought possible that the loss of calcium into the gut might be stemmed by raising the concentration of calcium in the gut lumen, and that serum calcium might be increased. A daily intake of 2·2 g. (Case 9) was without effect upon the balance. The role of parathormone is difficult to assess. Certainly, in the present series, the high level of faecal calcium, normal serum calcium and increased inorganic phosphorus, and the results of bone biopsy and radiography, do not support the theory of hyperparathyroidism. That bone destruction may ultimately occur in some cases seems to be certain (von Recklinghausen, 1891; Martos, 1938; Askanazy and Rutishauser, 1933; Follis, 1953). In addition, there have been several references to hyperparathyroidism in association with thyrotoxicosis. Aarseth and Bjørgo (1949) reported a parathyroid tumour; Noble and Borg (1936) recorded hyperparathyroidism and thyrotoxicosis in one case; Miller and Evans (1942) described hypercalcaemia in association with thyrotoxicosis; and a similar case was described by Rose and Boles (1953).

The increase of serum inorganic phosphorus is very striking, and the possibility that bone changes in thyrotoxicosis are the result of a primary disturbance in phosphorus metabolism seems to warrant further investigation. Engfeldt and Hjertquist (1954) noted that feeding thyroid to rats caused an increase in serum inorganic phosphorus, and that there was an increase in parathyroid activity judged histologically. Alteration in the level of serum inorganic phosphorus also occurs in post-menopausal and senile osteoporosis, and during periods of active skeletal growth. It has been suggested that this elevation might be due to excessive anterior pituitary activity. In the former conditions, at least, it is inhibited by stilboestrol or testosterone. Thyrotoxicosis may be primarily a disease of the pituitary, and an explanation of the disordered metabolism of bone might lie in this fact.

We are grateful to our nursing staff under the supervision of Sister D. T. Fraser; to Dr. Peter Walker, biochemist to the Institute; to our dieticians, Miss Jean McLelland, Mrs. R. Neill, and Miss Hilb; to the hospital consultants and local general practitioners who referred patients; and to Dr. A. W. Goolden, who undertook the radioactive iodine studies and therapy. Some of the work concerned in this paper has been included in a thesis by P. B. C. accepted for the degree of M.D., University of London.

APPENDIX

Abstract of Clinical Notes

Case 1. A joiner of 38 years. He complained of loss of weight, trembling, and perspiration. Symptoms had been present for four months. He had an enormous appetite, and noticed weakness in his arms. Examination revealed a very thin man, with lid lag and lid retraction. The pulse rate was 120; there was wasting of the supraspinati, and slight diffuse enlargement of the thyroid.

Case 2. A housewife of 34 years. She had had diarrhoea, loss of weight, tremor, and perspiration, for one year. Menstruation was very scanty. Examination showed lid lag and lid retraction, enlargement of the thyroid, and a thyroid hum. The skin was moist, and there was a fine tremor of the fingers.

Case 3. A truck driver of 25 years. He had noticed swelling of the neck three years previously. He had been treated with methyl thiouracil, and remained well until four months before admission. He then noticed increased swelling in the neck, sweating, tiredness, loss of weight, breathlessness, and diarrhoea. The thyroid was found to be enlarged, with tremor of the fingers, lid retraction, and a pulse rate of 94. Muscular power in the arms was poor, and there was wasting of the supraspinati.

Case 4. A female clerk of 29 years. She had lost weight, in spite of an enormous appetite, for the previous three months, and had diarrhoea, perspiration, tiredness, and tremor of the fingers. She gave a history of tuberculosis of the spine and hip. Arthrodesis of the hip had been performed four years ago, but the patient had been fully ambulant since that time. Examination revealed enlargement of the thyroid gland, a moist skin, and tremor.

Case 5. A schoolgirl of 16 years. She had had swelling of the neck, an enormous appetite, and breathlessness upon slight exertion, for one year. The thyroid was diffusely enlarged, and a thyroid hum was present. The pulse rate was 110; there was marked tremor of the fingers.

Case 6. A builder of 51 years. He had noticed swelling of the neck for two years. At that time a diagnosis of thyrotoxicosis had been made and treatment commenced with methyl thiouracil, which caused a sore throat and leucopenia. Improvement followed rest in bed and phenobarbitone. Recently restlessness and excessive thirst caused the patient to seek further advice; perspiration and periodic diarrhoea also developed. Examination revealed diffuse thyroid enlargement, tremor, lid lag, and a pulse rate of 90.

Case 7. A housewife of 44 years complained of swelling of the neck, tiredness, and loss of weight, for the previous four months. Examination revealed an enlarged thyroid, tremor of the fingers, and a pulse rate of 100.

Case 8. A housewife of 57 years complained of loss of weight and staring eyes for the previous three months. There had been a loss of three stone in weight. Palpitations, perspiration, enormous appetite, and faintness after exertion were also present. Examination revealed a pulse rate of 82 with frequent extrasystoles, slight diffuse enlargement of the thyroid, marked lid retraction, and lid lag.

Case 9. A housewife of 44 years complained of shaking of the hands, swollen eyelids, and prominent eyes; the symptoms had been present for three months. Bowel motions were frequent, perspiration was excessive, and breathlessness followed the slightest exertion. On examination the pulse rate was 120; the thyroid gland was diffusely enlarged, and there was marked lid retraction and lid lag.

Summary

The results of balance studies for calcium, phosphorus, and nitrogen in nine cases of thyrotoxicosis are recorded. The studies are supplemented by the results of serum analysis and faecal fat estimation. Studies were prolonged, and include the results of treatment with thiouracil and radioactive iodine. The main findings were a universally negative calcium balance due to increased faecal calcium, often in excess of intake, and increased urinary calcium. Faecal fat was above normal limits. Serum inorganic phosphorus was increased, and also serum alkaline phosphatase. The effect of treatment was to restore a positive calcium balance, reduce faecal fat, and reduce serum inorganic phosphorus to normal levels. The serum alkaline phosphatase was further increased.

Bone biopsy was performed in each case, and showed histological evidence to support a diagnosis of osteoporosis in a majority of cases, but no evidence of excessive bone destruction.

The effects of vitamin D have been studied, with varying intake of calcium and anabolic hormones. Theories of causation are discussed.

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RENAL ABNORMALITIES IN THE MARFAN SYNDROME[1]

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With Plates 33 to 35

CONGENITAL abnormalities of the heart, great vessels, and lungs are well known accompaniments of the Marfan syndrome, a condition recognized by certain striking external features. These include muscular hypotonia, elongation of the fingers and toes or 'arachnodactyly', a high-arched palate, and dislocation of the optic lenses. Recently the occurrence and clinical significance of congenital renal anomalies in the syndrome have also been demonstrated (Booth, Loughridge, and Turner, 1957). Of the two patients described, polycystic kidneys occurred in the first, a man of 33 years, and in the second, a boy of 16 years, bilateral chronic pyelonephritis with unilateral hydronephrosis and hydroureter. The latter findings were associated with an unexplained, non-inflammatory ureteral obstruction on the same side. The cause of death in both patients was chronic renal failure with azotaemia. The importance of anomalies of the genito-urinary tract in this syndrome had not previously been emphasized.

In a review of more than 200 recorded cases of the Marfan syndrome, Rados (1942) stated that involvement of the genito-urinary system had not been described. Genital hypoplasia and undescended testes had, however, been recorded (Börger, 1914; Delord and Viallefont, 1936; Haridas, 1941), and Olcott (1940) had described a patient with an ectopic left kidney. Later Stern (1944) referred to the occurrence of undescended testes in subjects with arachnodactyly, and Moehlig (1949) listed small kidneys with the more commonly recognized features of the Marfan syndrome. No details of these renal anomalies were recorded. Fischl and Ruthberg (1951) described a patient in whom an ectopic and hydronephrotic left kidney was found; post-mortem examination of a further patient recorded by Whitfield, Arnott, and Stafford (1951) revealed enlargement of the kidneys, with widening of the glomerular spaces and debris in the tubules. These changes, however, were attributed to passive congestion of the kidneys, as the patient died in heart failure secondary to a diffuse myocarditis. McKusick (1955) stated that two of his patients with the Marfan syndrome, aged 27 and 25 years respectively, appeared to have essential hypertension, and he referred to a third who had malignant hypertension. Details of renal function were not recorded. In a patient with long-standing

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hypertension, described by Dexter, Lawton, and Warren (1957), bilateral dilatation of the renal pelves, with double pelves and calyces on one side, was demonstrated on intravenous pyelography. The present paper records clinical details of eight patients with renal involvement in the Marfan syndrome. In seven patients functional impairment of the kidneys was of major clinical importance, and one of these has died from her renal disease. The post-mortem

TABLE I

Summary of Renal Lesions

Case number	*Age*	*Sex*	*Blood pressure (mm.Hg)*	*Renal function*	*Intravenous pyelography*	*Clinical diagnosis*
1	16	F	210/160	Proteinuria; pyuria, with coliform organisms on culture. Terminal blood urea 400 mg./100 ml.	Asymmetry of renal size. Bilateral clubbing of calyces	Chronic pyelonephritis with malignant hypertension
2	19	F	170/125	Proteinuria; pyuria, with staphylococci on culture. Blood urea 27 mg./100 ml. G.F.R. 121 ml./min. E.R.P.F. 300 ml./min. Filtration fraction 41%. Impaired urinary acidification	Bilateral clubbing of calyces	Chronic pyelonephritis with hypertension
3	14	M	170/110	Proteinuria. Blood urea 65 mg./100 ml. G.F.R. 30 ml./min. E.R.P.F. 90 ml./min. Filtration fraction 35%	Bilateral clubbing of calyces with ureteric dilatation	Chronic pyelonephritis with hypertension
4	7	M	150/100	Proteinuria. Blood urea 27 mg./100 ml. Maximum urine sp. gr. 1,015	Ectopic left kidney	Renal ectopia. Chronic pyelonephritis with hypertension
5	19	F	120/65	Proteinuria; pyuria, with *Bact. coli* on culture. Blood urea 22 mg./100 ml.	Double right kidney and ureters with partial dilatation of calyces	Duplex kidney. Recurrent unilateral acute pyelonephritis
6	50	F	210/115	Proteinuria. Blood urea 42 mg./100 ml.	Poor dye excretion by left kidney	Chronic pyelonephritis (? unilateral) with hypertension
7	54	M	280/140	Blood urea 26 mg./100 ml.	Double right kidney and ureter. Absent left kidney	Duplex kidney. ? Chronic pyelonephritis with hypertension
8	29	F	110/75	Blood urea 27 mg./100 ml. on recovery from acute renal failure	Double right kidney and ureter	Duplex kidney. Acute oliguric renal failure following abortion

G.F.R. = glomerular filtration rate. E.R.P.F. = effective renal plasma flow.

findings in this case are recorded. In the remaining patient the structural renal anomaly appears to have no functional significance. In three instances discovery of an asymptomatic renal lesion resulted from recognition of the external features of the Marfan syndrome, with subsequent investigation of the renal tract. In one of these three patients, a sibling of an earlier patient in the series, unsuspected kidney disease was revealed during a routine assessment of the family for features of the Marfan syndrome and evidence of renal malfunction.

Case 1. A 16-year-old female shop-assistant was admitted to St. Nicholas' Hospital, Plumstead, on 2.5.57, with a diagnosis of acute intestinal obstruction. In addition she was found to have severe hypertension, with bilateral

TABLE II

Summary of Features of the Marfan Syndrome

Case number	*Facies*	*Palate*	*Extremities*	*Eyes and ears*	*Patellar ligaments*	*Height*	*Arm span*	*Crown-to-pubis measurement*	*Pubis-to-ground measurement*	*Other features*
1	Long face with marked prognathism	High-arched	Striking elongation of fingers and toes	Normal	2″	66″	68½″	32″	34½″	'Droopy' appearance with muscular hypotonia. No heart murmurs or thoracic deformity
2	Long face with prognathism. Striking resemblance to Case 1	High-arched	'Spider' fingers and toes	Normal	2″	67″	70″	31″	36″	Muscular hypotonia. No heart murmurs or thoracic deformity
3	Long face. No prognathism	High-arched	Fingers and toes not markedly elongated	Concomitant strabismus	2½″	68½″	71″	32½″	35½″	'Droopy' appearance with poor muscular development. 'Funnel' chest deformity. No heart murmurs
4	Long face with marked dolichocephaly	High-arched	'Spider' fingers and toes	Bilateral lens dislocation. Bilateral glaucoma. Long pointed ears	1½″	51″	54″	23½″	27½″	Very poor muscular development. No heart murmurs or thoracic deformity
5	Long face	High-arched	'Spider' fingers and toes	Normal	2½″	69″	71″	34″	35″	Moderate muscular development. No heart murmurs or thoracic deformity
6	Long face with prognathism	High-arched	'Spider' fingers and toes	High degree of myopia	2½″	71″	72″	34½″	37½″	'Droopy' appearance with marked muscular hypotonia. Apical systolic murmur. No thoracic deformity
7	Long face	High-arched	Moderate elongation of fingers and toes	Very prominent large ears	2½″	72″	72″	36″	36″	Features suggestive of early 'progressive muscular atrophy'. No heart murmurs or thoracic deformity
8	Long face with prognathism	High-arched	'Spider' fingers and toes	Normal	2½″	70″	73″	34″	36″	'Droopy' appearance with muscular hypotonia. No heart murmurs or thoracic deformity

papilloedema and heavy proteinuria. The blood urea was 49 mg. per 100 ml., and haemoglobin 8·6 g. per 100 ml. At operation five feet of gangrenous terminal ileum were resected, and on palpation the left kidney was found to be considerably smaller than the right. Post-operative ileus was associated with severe oliguria and azotaemia; the blood urea later fell to 68 mg. per 100 ml. An intravenous pyelogram at this stage showed some excretion of dye by the right kidney, but little by the left. A tentative diagnosis of polyarteritis nodosa was made, and the patient was transferred to Hammersmith Hospital for treatment of her hypertension. A past history of painless frequency of micturition was obtained; there had been no episode suggestive of acute glomerulonephritis. On examination she was tall, thin, and kyphotic, with a markedly 'droopy' appearance, and the characteristic facies, high-arched palate, and long fingers and toes of the Marfan syndrome (Plate 33, Figs. 1 and 2). Muscular development was poor, and there was striking hypotonia. These and other skeletal features are summarized in Table II. The blood-pressure was 210/160, and papilloedema persisted. Pyuria was associated with a growth of coliform organisms on urine culture. The blood urea remained at 60 mg. per 100 ml. A clinical diagnosis of malignant hypertension secondary to probable chronic pyelonephritis was made, though a unilateral renal vascular lesion seemed possible in view of the asymmetry of kidney size. A partial dissection of the abdominal aorta was considered as a possible explanation of the recent acute episode. Treatment with antihypertensive drugs achieved moderate blood-pressure control, and the patient remained free of symptoms until 25.2.58, when she was readmitted with a further episode of intestinal obstruction. At operation two feet of gangrenous proximal small bowel were resected, and afterwards her general condition rapidly deteriorated. The blood-urea level rose to 400 mg. per 100 ml., and she died shortly after the onset of severe, generalized epileptiform convulsions.

Post-mortem examination (Dr. I. Williams) was carried out 24 hours after death.

Macroscopic findings. The lungs showed gross pulmonary oedema, with generalized bronchopneumonia, and pus in the main bronchi, trachea, and larynx. There was no evidence of pericarditis, but petechial haemorrhages were noted on the surface of the heart at its base. The heart weighed 330 g., with dilation and hypertrophy of the left ventricle. The valves and coronary arteries appeared normal. The aorta, throughout its length, was noted to be hypoplastic for the patient's age. No evidence of dissection could be detected, and there was no asymmetry or abnormality of the renal or other branches. The liver was enlarged and congested; the gall-bladder, spleen, and pancreas appeared normal. Recent adhesions were found between loops of small bowel. No abnormality of the thyroid, pituitary, or adrenal glands was observed. The previously noted asymmetry in renal size was confirmed, the right kidney weighing 120 g. and the left 60 g. On the right side the capsule stripped with difficulty to reveal a very irregular surface, with yellowish-white raised areas separated from each other by depressed scars (Plate 33, Fig. 3). On section the yellow areas were seen to extend from the surface to involve both cortex and medulla in irregular bands. The hilar vessels and pelvis appeared normal. There was reduction in thickness of the cortex, with blurring of the corticomedullary junction. A similar appearance was found on the left side, but scarring was more extensive.

Microscopic findings. There was evidence of chronic pyelonephritis in both kidneys, with crowding of hyalinized glomeruli, dilatation of tubules, and infiltration of lymphocytes round the damaged nephrons. In addition vascular

changes of hypertension were present, including proliferation of the intima of interlobular arteries and proliferation and medial hypertrophy of afferent arterioles. The fibrinoid necrosis of malignant hypertension was not seen. There were large fresh abscesses due to acute pyelonephritis in both kidneys.

Family history. Investigation of the patient's family was carried out at the time of her first admission to hospital. The parents were of average build, and showed none of the external features of the Marfan syndrome. Two of the patient's three sisters were tall and thin and had 'arachnodactyly', and one of them (Case 2) was found to have moderately severe hypertension. An intravenous pyelogram showed bilateral clubbing of the calyces suggestive of chronic pyelonephritis. Details of further investigations in this patient are given below (Case 2). The other 'affected' sister had a blood-pressure of 125/70 mm. Hg, and intravenous pyelogram showed no abnormality.

Case. 2. A 19-year-old counting-machine operator, sister of the first patient, was admitted to Hammersmith Hospital on 13.9.57 after the discovery of symptomless hypertension associated with radiological abnormality of the kidneys. She gave a history of nocturia of many years' duration, and at the age of 10 years had had several brief attacks of dysuria, for which she had received no treatment. There had been no episode suggestive of acute glomerulonephritis. On examination, she was tall and thin, with a similar 'droopy' appearance and striking facial resemblance to her younger sister (Case 1). In addition to a prominent lower jaw, she had a high-arched palate and long, 'spider' fingers and toes (Plate 34, Fig. 4). Her arm span exceeded her height by three inches, and the measurement from pubic symphysis to ground was greater than that from crown to symphysis by five inches. The optic lenses were not dislocated, and the ears were normal. The average blood-pressure reading in both brachial arteries was 170/125, and the femoral pulses were readily palpable. The heart was not enlarged, there was no evidence of heart failure, and the optic fundi showed arterial narrowing and arteriovenous nipping only. The lower pole of the left kidney was palpable. Examination of the urine revealed a moderate proteinuria on one occasion only, and there were numerous pus cells in the centrifuged urinary deposit. Culture of urine revealed a growth of a staphylococcus, which responded to treatment with oral sulphadimidine. The blood urea was 27 mg. per 100 ml., and the maximum urine specific gravity achieved after 12 hours' fluid restriction was 1,016. The serum electrolytes were normal. The kidney outlines were equal in size, and an intravenous pyelogram was consistent with symmetrical chronic pyelonephritis.

Renal clearance studies showed a glomerular filtration rate of 121 ml. per minute (inulin infusion technique), and effective renal plasma flow of 300 ml. per minute (*p*-aminohippurate infusion technique). The filtration fraction thus obtained was 41 per cent. A simultaneous endogenous creatinine clearance gave a glomerular filtration rate of 136 ml. per minute. An ammonium chloride test of tubular acidifying power showed a minimum urine pH of 5·92 two hours after the second of two oral doses of 4 g. of the salt. There was no glycosuria or abnormal aminoaciduria.

Despite the absence of symptoms referable to hypertension, treatment with antihypertensive drugs was given in an attempt to retard the rate of progress of the renal lesion, particularly in view of the grave family history. On a régime controlled by regular out-patient visits, this treatment was well tolerated by the patient, the average diastolic blood-pressure being maintained in the region of 100 mm.Hg. There had been no proteinuria, and the blood urea had remained normal, up to November 1958.

Case 3. A 14-year-old schoolboy was admitted to Hammersmith Hospital with a clinical diagnosis of infectious mononucleosis. He was found to have a blood-pressure of 170/110 mm.Hg, narrowing of the retinal arteries, and proteinuria; culture of the urine was sterile. He was tall, thin, and 'droopy', with the characteristic facies and gothic palate of the Marfan syndrome. There was a 'funnel' deformity of the chest. These and other features are summarized in Table II. Investigations showed a blood-urea level of 65 mg. per 100 ml., average serum potassium 2·5 m-equiv. per litre, and serum bicarbonate 31 m-equiv. per litre. Haemoglobin was 85 per cent. An intravenous pyelogram showed excretion of dye by both kidneys, which were normal in size and outline (Plate 34, Fig. 5). The calyces, however, were clubbed on both sides, with some ureteric dilation. Renal clearance studies showed a glomerular filtration rate of 30 ml. per minute (inulin infusion) and effective renal plasma flow of 90 ml. per minute (*p*-aminohippurate infusion) giving an elevated filtration fraction of 35 per cent. An ammonium chloride test of tubular acidifying power, as described in Case 2, showed a minimum urine pH of 5·5. There was no abnormal aminoaciduria, and no glycosuria at any time. The serum-potassium level remained persistently low, and was associated with a loss in the urine of 25 to 30 m-equiv. per 24 hours. The serum level, however, was readily restored to normal and maintained by oral supplements of potassium chloride. A final diagnosis of hypertension associated with symmetrical chronic pyelonephritis was made, with the added feature of a potassium-losing tendency considered to be due to a tubular defect.

Family history. Investigation of the patient's family revealed that the father was tall, with a high-arched palate but normal extremities. The patellar ligaments measured three inches, but other skeletal dimensions were normal. There was no proteinuria, and the blood-pressure was 140–90. The mother was of squat build, and had no features of the Marfan syndrome. An only brother, aged 31, was tall, but the palate, extremities, and skeletal proportions were normal. His blood-pressure was 135/80, and analysis of the urine revealed no abnormality.

Case 4. A seven-year-old boy was admitted to the Royal Belfast Hospital for Sick Children on 3.1.57, with a four-week history of attacks of abdominal pain and vomiting. In 1955 he had had an attack of acute glomerulonephritis, from which he had made a complete clinical recovery. During the intervening period of two years he had failed to attend hospital, but had apparently remained quite free from symptoms. On examination he was a thin, pale child with the characteristic dolichocephaly, long face, and bodily configuration of the Marfan syndrome. There was bilateral subluxation of the optic lenses, and the palate was high-arched. These features are summarized in Table II. The blood-pressure was 150/100, and the optic fundi showed arterial narrowing with arteriovenous nipping.

Analysis of the urine showed no protein, and there were no red blood-cells or pus cells in the centrifuged deposit. Urine culture was sterile. There was no anaemia, and the erythrocyte sedimentation rate was not elevated. Blood urea was 27 mg. per 100 ml., but the maximum specific gravity of the urine achieved after 12 hours' fluid restriction was only 1,015. An intravenous pyelogram showed a normally working right kidney with good concentration of the dye (Plate 35, Fig. 6.) There was evidence of dye being excreted on the left side by an abnormally situated kidney, lying on the left side of the pelvis at the level of the inferior margin of the sacro-iliac joint. Concentration from this ectopic organ appeared satisfactory. A retrograde pyelogram on the left

side showed no gross hydronephrotic changes, in spite of the abnormal position (Plate 35, Fig. 7). Only the lower calyces, however, were sharply defined. A diagnosis of hypertension associated with probable chronic pyelonephritis was made. Surgical removal of the ectopic kidney was not considered, in view of the apparent persistence of satisfactory function on that side and the possibility of bilateral disease. Treatment with antihypertensive drugs was deferred, because of the known lack of parental co-operation and resultant problems of dosage control in a young patient.

By November 1957 the blood-pressure had risen to 180/110, and was associated with subjective visual disturbance. On this occasion a moderate proteinuria was found, though no pus cells or bacteria could be demonstrated. The blood urea remained normal. In February 1958 the patient developed severe pain in the left eye, and on his readmission a diagnosis of glaucoma was made. This condition has subsequently become quiescent, but enucleation of the eye has been performed because of the risk of rupture of the globe. Acute glaucoma in the right eye has recently developed, and the ectopic lens has been removed. Treatment with apresoline and serpasil has achieved an average blood-pressure reading of 135/75.

Family history. Investigation of the patient's family failed to reveal features of the Marfan syndrome in either parent, or in the patient's five surviving siblings; two other children had died at an early age, from measles and convulsions respectively. The patient's father, aged 47, had an attack of acute glomerulonephritis in 1939, from which he retained slight residual proteinuria without hypertension or other evidence of renal malfunction.

Case 5. A 19-year-old girl was admitted to Hammersmith Hospital on 8.4.58, with a three-day history of pain in the right flank, dysuria, frequency of micturition, and fever. Similar attacks had occurred from the age of four years, becoming more frequent in the three months preceding her present admission. Nocturia had been noted throughout this period. The pain had invariably affected the right side. There was no history of facial or peripheral oedema. On examination she was tall and thin, with the long facies, high-arched palate, and long fingers and toes of the Marfan syndrome. Her arm span exceeded her height by two inches, and the measurement from pubic symphysis to ground was greater than that from crown to symphysis by one inch. The patellar ligaments each measured two and a half inches. The eyes and ears were normal, and there was no deformity of the thoracic cage. The blood-pressure was 120/65, and the heart sounds were normal. The lower pole of the right kidney was palpable. Muscular development was moderately good. Analysis of the urine showed a moderately heavy proteinuria, with pus cells in the centrifuged urinary deposit. A growth of *Bact. coli* was obtained on culture. She had pyrexia on admission, and the white-cell count was 14,000 per. cu. mm. There was no anaemia, and blood urea was 22 mg. per 100 ml. Serum electrolytes were normal. X-rays of the chest were normal.

Treatment with oral sulphadimidine achieved resolution of the fever and sterilization of the urine. An intravenous pyelogram during her recovery showed good excretion from both sides, with a normal calyceal pattern on the left (Plate 35, Fig. 8). On the right side there was a double kidney, with two ureters fused at the level of the transverse process of the fifth lumbar vertebra. The calyces of the upper element and the superior calyces of the lower element were dilated, while the remainder had a normal appearance. In the absence of hypertension, and renal function being satisfactory on the affected side, surgical treatment was not considered, and a long-term course of oral

sulphamethoxpyridazine (0·25 g. three times per week) was started before the patient's discharge.

Family history. Assessment of the patient's family revealed that the father, who had died at the age of 61 from bronchial carcinoma, and the mother, aged 57, were both of average build. The eldest sister, aged 29, was found to be attending Hammersmith Hospital with recurring pyelonephritis, in association with a complete double kidney and ureters on the right side and considerable calyceal dilatation (Plate 35, Fig. 9). In addition, on the left side there was a small cyst in communication with the superior calyx, probably of congenital origin. On examination she was tall, though of broader build than her sister (Case 5). The palate was normal, and the fingers were not unduly elongated. Arm span and height were equal, but the measurement from pubic symphysis to ground exceeded that from crown to symphysis by two and a half inches. The ears, eyes, and thoracic cage showed no abnormality. The youngest sister, aged 15, had had intermittent pain in both loins, with frequency of micturition, since early childhood. She was stated to be abnormally tall for her age, but was not available for examination. The three remaining male siblings, who were not available for assessment, were described as tall and thin, but quite free from symptoms.

Case 6. A 52-year-old single female clerk was admitted to Hammersmith Hospital in March 1956, with a unilateral retinal artery thrombosis, in association with hypertension for which she had been receiving treatment. Two years previously a diagnosis of hypertension, possibly secondary to chronic pyelonephritis, had been made, in view of a long history of nocturia with attacks of loin pain and dysuria. On examination she was very tall and thin, with the characteristic long facies and 'droopy' appearance of the Marfan syndrome. The palate was high-arched, and there was striking elongation of the fingers and toes. These features are summarized in Table II. Investigations showed the presence of proteinuria, with a sterile urine culture. Blood urea was 42 mg. per 100 ml. An intravenous pyelogram showed satisfactory excretion of dye from the right kidney. On the left side excretion was poor, and the pelvis and calyces were deformed and not well defined. Appearances suggested unilateral pyelonephritis. Satisfactory control of blood-pressure is at present achieved with oral mecamylamine. A trace of protein persists in the urine.

Family history. Assessment of the patient's family revealed that the father was of average build, but had died suddenly at the age of 39 from heart disease. The patient's mother, of similar build, had died from pneumonia at the age of 44. Of the two siblings, the sister, aged 58, was very tall and thin, and had long fingers and toes. These features were so striking that they had often been noticed by members of the family, and the two sisters were considered quite unlike the rest of the family. The patient's brother, though tall, was not of slender build, and the extremities not elongated. His blood-pressure was normal.

Case 7. A 54-year-old male stock-keeper was admitted to Hammersmith Hospital on 2.1.58 for assessment of hypertension. He gave a past history of nocturia for many years, but had had no dysuria or loin pain at any time. On examination, he was tall and thin, with a 'limp' appearance and the characteristic elongated facies of the Marfan syndrome. A striking feature was the prominence of his ears, which were large but normal in shape. The palate was high-arched, and the fingers and toes were long. The patient's height and arm span were each 72 inches and the measurements from symphysis pubis to ground and

from crown to pubis were also equal. The patellar ligaments measured two and a quarter inches. There was no deformity of the thoracic cage, and the optic lenses were not dislocated. The blood-pressure was persistently raised, with an average reading of 280/140. The cardiac apex was not displaced, no murmurs were heard, and there was no evidence of heart failure. The femoral pulses were readily palpable. The optic fundi showed arterial narrowing and arteriovenous nipping. Examination of the nervous system suggested the possibility of early progressive muscular atrophy. Analysis of the urine revealed no protein, and there were no pus cells or red blood-cells in the centrifuged deposit. Culture was sterile. There was no anaemia, and chest X-rays were normal. Blood urea was 26 mg. per 100 ml., with normal serum electrolytes. An intravenous pyelogram showed good excretion from a double kidney on the right side. On the left side no excretion of dye could be seen and no renal outline defined. On cystoscopy no ureteric orifice was visible on the left, while on the right two orifices were found, the lower of which was small and very difficult to catheterize. A retrograde pyelogram showed filling of two apparently separate renal pelves, each with a normal appearance, on the right side. Divided renal function studies were not attempted because of the technical difficulty of inserting a ureteric catheter into the smaller orifice. Treatment with antihypertensive drugs was started, and satisfactory control achieved before the patient's discharge.

Family history. Assessment of the patient's family revealed that both parents, and the patient's only brother, were of medium build, with no external evidence of the Marfan syndrome. His daughter, aged 12 years, was of squat build. There was no known family history of renal disease or hypertension.

Case 8. A 29-year-old woman was admitted to Hammersmith Hospital on 9.8.57 for treatment of acute oliguric renal failure following a procured septic abortion. No preceding history of renal disease was obtained. On examination she presented striking external features of the Marfan syndrome, including 'spider' fingers and toes, a high-arched palate, long facies with protrusion of the lower jaw, and marked muscular hypotonia. These and other features are summarized in Table II. The blood-pressure was 110/75. Severe azotaemia, acidaemia, and hyperkalaemia necessitated treatment by haemodialysis with an artificial kidney, and the patient subsequently made an uneventful recovery. An intravenous pyelogram in the convalescent phase showed good concentration of dye on both sides, with a double kidney and ureter on the right. There was no evidence of residual renal malfunction. The relatives of this patient were not examined.

Discussion

Renal abnormalities in the Marfan syndrome are of considerable clinical significance. Each of the patients described in this paper had some defect of one or both kidneys and, in all but one instance, this defect was of major functional importance (Table I). In three patients (Cases 2, 3, and 7) discovery of previously unsuspected asymptomatic disease of the kidneys followed investigation which was prompted solely by recognition of the external features of the Marfan syndrome. Two of these patients (Cases 2 and 7) are now receiving antihypertensive treatment with benefit. Renal lesions occurring in more than one member of a given kinship have been demonstrated twice in this series

(Cases 1 and 2; Case 5), and it is therefore of value to assess kidney function in 'affected' members of such families. These findings emphasize two points: first, the importance of recognition of features of the Marfan syndrome in patients with obscure renal disease, since an underlying congenital anomaly may be discovered; and second, the value of investigation of the renal tracts of subjects with the Marfan syndrome, since unsuspected kidney disease, amenable to treatment, may be revealed.

To Marfan's (1896) original description of a five-year-old child with poor musculature and 'spider' fingers, other features have been added to constitute a clinical syndrome. Such features include a narrow, high-arched or 'gothic' palate, dolichocephaly with a characteristic long face and prognathism of the lower jaw, elongated and sharply pointed ears, and dislocation of the optic lenses. Poor skeletal muscular development, with hypotonia and a tendency to 'droop', is characteristic, as are undue elongation of the fingers and toes, or 'spider' digits. Attempts to define the limits of 'arachnodactyly' have been few, but it has been suggested that an excess of 50 per cent. of total phalangeal over corresponding metacarpal or metatarsal length is diagnostic. These measurements can be made satisfactorily only from X-rays of the hands and feet. Certain other skeletal features have been described; these include an excess of arm span over total body height, and of the measurement from pubic symphysis to ground over that from crown to symphysis. Laxity of ligaments has often been emphasized, and the patients have a tendency to 'double-jointed' thumbs, while partial subluxation at the knees may lead to a characteristic genu recurvatum. Excessively long patellar ligaments have been described. Definition of the normal length of the patellar ligament has been attempted, and it has been reported that the mean distance from the lower border of the patella to the summit of the tibial tubercle in 25 normal subjects was 1·4 inch, with a maximum value of 1·8 inch (Booth, Loughridge, and Turner, 1957). Other external features include deformities of the thoracic cage, irregularities of the teeth, prominent supraorbital ridges, wide-apart eyes, and a disproportionate elongation of the ring fingers and great toes.

In the present series considerable diagnostic importance was given to the characteristic long facies with prognathism, and to the bodily configuration with 'droopy' appearance and poor musculature. A high-arched palate was a very constant feature, but ectopia lentis occurred in only one instance. Excessive length of the patellar ligaments was considered a valuable sign, as were the other skeletal measurements already described. Clinical 'arachnodactyly' was present in six of the eight patients. These findings are summarized in Table II. The use of a single manifestation, 'archnodactyly', to describe the syndrome was rejected by McKusick (1956), who preferred the title 'the Marfan syndrome'. In support of this contention he claims that the fingers may not always be 'spidery'; for example, if the syndrome occurs in previously pyknic stock, undue elongation of the extremities is less likely, and other features then lead to the diagnosis.

The nature of the renal lesion in the present series of patients varied. In

some it was a structural anomaly of undoubted congenital origin (Cases 4, 5, 7, and 8); in others the congenital basis of the defect was less obvious (Cases 1, 2, 3, and 6). In Cases 1 and 2, however, the familial occurrence of chronic pyelonephritis with hypertension at an early age seems significant, and may imply some congenital factor predisposing to renal infection. McKusick (1956) has suggested, in the case of other mesenchymal organs involved in the Marfan syndrome, that a tissue abiotrophy results in increased vulnerability to environmental factors. Goldbloom, Fraser, Waugh, Aronowitch, and Wigglesworth (1957), in a review of hereditary renal disease, referred to the possibility of increased tissue susceptibility due to multifocal hypoplasia or malformation. Marshall (1956) has advanced the theory that renal scarring occurs in foci of maldeveloped tissue. An inherited tissue-enzyme defect has been suggested. Recognition of the association of renal disease, of the type seen in Cases 1 and 2, in the Marfan syndrome adds support to the view that congenital hypoplasia may be important in the development of pyelonephritis. Though no pyelographic deformity is diagnostic, Emmett, Alvarez-Ierena, and McDonald (1952) have suggested that cases of apparent 'chronic atrophic pyelonephritis' may develop on a primary basis of congenitally small kidneys.

The dominant mode of inheritance of the Marfan syndrome was first demonstrated by Weve (1931). McKusick (1956), confirming this finding in 85 per cent. of cases, stated that the remaining 15 per cent. arose as a *de novo* mutation. The phenomenon of 'skipped generations' was accounted for by the wide variability of clinical expression in the syndrome. In a recent study Lynas (1958) has shown no evidence of consanguinity, and suggests that the condition is inherited as a dominant trait acting irregularly. Many references to hereditary factors in renal disease, and to associated skeletal and other features, are available in the literature. These clinical syndromes are described in a review of the hereditary aspects of chronic renal disease (Robin and Gardner, 1957), but no reference is given to features suggestive of the Marfan syndrome. Early examples of the congenital and familial occurrence of 'chronic Bright's disease' (Dickinson, 1875; Pel, 1899) and 'idiopathic familial haematuria' (Gutherie, 1902) are quoted. The kinship recorded by Gutherie was later reviewed (Hurst, 1923), and the condition re-named 'hereditary, familial, congenital haemorrhagic nephritis'. Of the 28 members investigated 16 were affected by 'nephritis', and the condition was more lethal in the male and apparently transmitted only by the female subjects. Perkoff, Stephens, Dolowitz, and Taylor (1951) gave the first definite evidence of hereditary pyelonephritis in a study based on 232 descendants of one person. Previously recorded cases had been grouped either as glomerulonephritis or as unclassified chronic renal disease. A high incidence of nerve deafness was recorded in affected subjects of this study. Again it was found that progressive renal failure occurred only in the male, and the condition was apparently transmitted as an incompletely sex-linked dominant. In 1954 a heredo-familial syndrome characterized by renal disease, inner ear deafness, and ocular changes, was described by Sohar. A further report on congenital hereditary haematuria was given in the same

year by Reyersbach and Butler. In 1956 Sturtz and Burke again recorded the association of hereditary haematuria, nephropathy, and deafness. A kinship of which four members were affected by 'renal dysplasia', in association with multiple hereditary abnormalities, was reported by Hawkins and Smith in 1950. The renal lesion, clinically, was thought to resemble a chronic glomerulonephritis, possibly more benign than the acquired form. The associated anomalies included iliac horns, absent or rudimentary finger-nails, absent patellae, and deformity of the elbow joints characterized by an increased carrying angle. In addition, pigeon-chest, cutaneous angiomata, cervical spina bifida, and polydactyly were noted. The triad of absent finger-nails, absent patellae, and abnormal elbows was considered to be the result of a single dominant gene. Goldbloom, Fraser, Waugh, Aronowitch, and Wiglesworth (1957) described a family in which the mother and three sons were affected by progressive renal disease, perceptive deafness, and ocular lesions including spherophakia and cataract. Again the partially sex-linked, probably dominant inheritance was stressed, and it was suggested that renal disease and deafness may be due to the same gene.

Hilson (1957) has drawn attention to a group of subjects in whom renal anomalies, including renal agenesis and polycystic kidneys, are associated with malformations of the external ear. Long and sharply pointed ears have been described in the Marfan syndrome, and were a striking feature of Case 7 of the present series. The large, folded, or 'Jumbo' ears of Hilson's description, however, have not been recorded in this syndrome. Reference to facial abnormalities in renal agenesis had previously been made by Potter (1946) and by Frankin and Marz (1954). Congenital renal abnormalities have been recorded in the Ehlers-Danlos syndrome, a condition characterized by a striking hyperelasticity and excessive fragility of the skin. McKusick (1955) grouped this, with the Marfan syndrome, as a hereditable disorder of connective tissue. Further resemblance lies in the high incidence of dissecting aneurysm, 'arachnodactyly', congenital heart disease, and herniae, in both conditions.

The aetiology of the Marfan syndrome is unknown. Early interpretations of the condition included that of Weve (1931), who explained the then recognized features on the basis of a congenital mesodermal dystrophy. 'Arachnodactyly' alone has occurred after intra-uterine rubella infection, in association with the more usual features of deafness with ocular and cardiac defects (McKusick, 1955). Cases simulating the Marfan syndrome have been reported to follow the occurrence during pregnancy of an unspecified febrile illness (Ganther, 1927), and also X-ray therapy (Stettner, 1937). Stewart's (1957) suggestion of a possible link between abnormal ears, anomalies of the renal tracts, and Rhesus blood groups, is interesting in view of the fact that 'arachnodactyly' has been reported to result from Rhesus incompatibility (McKusick, 1956). Experimentally, an acquired syndrome has been produced in the rat by the ingestion of a diet containing a large amount of the seed of the sweet-pea, *Lathyrus odoratus* (Ponseti and Shepard, 1954; Geiger, Steenbock, and Parsons, 1952). The features produced included kyphoscoliosis, hernia, and dissection of the

aorta, but 'arachnodactyly' apparently did not occur. Damage to the kidneys has not been recorded in these experiments, though testicular atrophy has been described.

The purpose of the present paper is to draw attention to the occurrence and functional significance of renal anomalies in the Marfan syndrome, and to stress the possibility of their incidence in other 'affected' members of a given kinship. The familial nature of the syndrome was first reported by Achard (1902). Rados recorded a positive family history in at least a quarter of patients, and McKusick later observed that the expression of the syndrome appears to be similar in affected members of any single family. This tendency to 'breed true' may be of particular importance in the earlier recognition of asymptomatic renal disease amenable to treatment. It is suggested that a brief assessment of kidney function should be carried out in all subjects with the Marfan syndrome. Where abnormalities are found, screening of the patients' families for features of the syndrome is advisable, with investigation of the renal tracts of 'affected' members.

I wish to thank Dr. M. D. Milne for encouragement and help in the preparation of this paper, and Professor J. McMichael and Dr. C. L. Cope for advice and criticism; also Professor F. M. B. Allen, Dr. J. G. Scadding, Dr. C. M. Fletcher, Dr. S. B. Karani, and Mr. R. Shackman for permission to publish details of patients who were under their care.

Summary

Eight patients with the Marfan syndrome and abnormalities of the kidneys are described. The clinical importance of this association is emphasized, and the value of assessment of renal function in such subjects and in their families is stressed.

The relationship of this to other forms of hereditary and familial renal disease is discussed.

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FIG. 1. Case 1. Long fingers of the Marfan syndrome. The hands of a normal subject are on the right

FIG. 2. Case 1. Posture characteristic of the Marfan syndrome

FIG. 3. Case 1. External surface of the right kidney, showing acute abcesses and scarring

FIG. 4. Case 2. 'Arachodactyly'. The hands of a normal subject are shown on the right

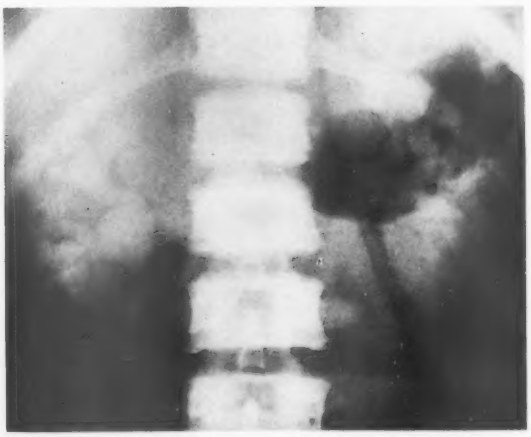

FIG. 5. Case 3. Intravenous pyelogram, showing bilateral 'clubbing' of the calyces

FIG. 6. Case 4. Intravenous pyelogram showing ectopic left kidney

FIG. 7. Retrograde pyelogram showing ectopic left kidney

FIG. 8

FIG. 9

FIGS. 8 and 9. Intravenous pyelograms to show the congenital anomaly of the right kidney in Patient No. 5 and in her sister

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CONGENITAL BICUSPID AORTIC VALVES AND THE AETIOLOGY OF ISOLATED AORTIC VALVULAR STENOSIS[1]

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With Plates 36 to 38

In a previous study three cases of combined aortic valvular stenosis and coarctation of the aorta were reported, and to these were added a further 24 post-mortem cases from the literature. In 20 there was a bicuspid aortic valve (Smith and Matthews, 1955). It was concluded that the aortic stenosis was due in many instances to degenerative changes in the bicuspid valve, hastened by the abnormal function of the malformed cusps and the high pressure to which, with coarctation, they are exposed. The present study was undertaken in order to determine whether malformations of the aortic valve, in particular bicuspid aortic valves, might be the underlying cause in some cases of aortic stenosis in a wider context, particularly in old age.

Material and Methods

Specimens of bicuspid aortic valves were examined from nine pathological museums of London, Guy's Hospital (G.), Hammersmith Hospital (H.), the London Hospital (L.), the Royal College of Surgeons (S.), St. Bartholomew's Hospital (B.), St. Mary's Hospital (M.), St. Thomas's Hospital (T.), University College Hospital (U.), and Westminster Hospital (W.). In referring to specimens the Hospital letter is prefixed to the museum number, for example, B. E.17 (specimen No. E.17 at St. Bartholomew's Hospital); where a number stands alone it refers to the order of specimens in Table II. As in most cases it was impracticable to remove the specimens from their containers, no histological examination was possible, and the gross appearances only are described. Where there was a report of the post-mortem examination, this was consulted and relevant details included in the analysis.

There were 55 specimens in all. In 53 there appeared to be only two cusps to the aortic valve, and in two more there was in addition a diminutive third cusp. By a process of elimination described in Table I the number was reduced to 28 specimens in which the abnormality could be regarded as congenital with as much certainty as can be attained without histological examination, and in

[1] Received January 13, 1959.

which the age and sex of the subject were known. In 24 of the 28 the cusps were approximately equal in size, in two of these there was in addition a diminutive third cusp. To these were added a further four (4, 6, 17, 18) in which the major cusps were unequal. They were included because there was an accompanying congenital abnormality, and we felt that this was strong supporting evidence that the aortic valve abnormality was also congenital. With these four exceptions, specimens in which the two cusps were unequal were excluded, because naked-eye inspection cannot be relied upon to distinguish between a

TABLE I

Bicuspid Aortic Valves: Selection of Specimens

Total number of specimens		55
History of rheumatic fever:		
H. 14.34.8; T. 1A.5.16; W. 01771; W. 04312	4	
Abnormality of the mitral valve (other than subacute bacterial endocarditis alone):		
L. 48; H. 14.34.11	2	
No information as to age and sex	7	
Inequality of the major cusps (with the exception of 4 specimens with an accompanying congenital anomaly:		
H. 14.12.6; H. 14.18.9; M. 14.14.2; T. 1A.1.17)	14	
	—	27
	Final series	28

congenitally bicuspid aortic valve with unequal cusps and a tricuspid valve with two of the cusps fused. When there was a ridge on one of the two cusps extending from the aortic wall toward the free margin of the cusp, microscopic examination might have revealed, in some of these cases, whether such a ridge represented the line of fusion of two cusps after birth, or an abortive third commissure. If there was a history of rheumatic fever the specimen was rejected. Specimens with abnormalities of the mitral valve were also excluded, unless the abnormality was clearly congenital (7) or consisted only of subacute bacterial endocarditis which had spread from the aortic valve (2, 21). It is a reflection of the inadequacy of museum material that seven specimens had to be excluded because there was no record even of the age and sex.

The analysis which follows is made from the series of 28 specimens of bicuspid aortic valves. In each of these specimens the following features were recorded: age at death, sex, accompanying congenital anomaly, the presence or absence of a ridge, thickening of the cusps, calcification of the cusps, fusion of the commissures, subacute bacterial endocarditis, and whether or not there appeared to be aortic stenosis. The specimen was labelled as showing aortic stenosis if it seemed from the appearance of the cusps that there had been significant obstruction to blood-flow. Although in many cases there was the characteristic concentric left ventricular hypertrophy of aortic stenosis, or a note of the clinical evidence of aortic stenosis from the patient's records, the material did not permit a complete analysis. Many of the specimens had been placed in the museums as examples of aortic stenosis, rather than as bicuspid aortic valves.

The incidence of the different varieties of specimen, of course, depends on the whim of the pathologists who decided to include them in the museum, as well as on the relative incidence of the diseases. An analysis was also made of all the specimens of aortic stenosis in these museums, in order to determine the proportion of them which were bicuspid.

TABLE II

Congenital Aortic Bicuspid Valves

Specimen number	*Museum and No.*	*Age of patient (years)*	*Sex of patient*	*Features of the cusps*							
				Size	*Thickening*	*Calcification*	*Ridge*	*Fusion of Commissure*	*Subacute bacterial endocarditis*	*Aortic stenosis*	*Accompanying anomaly*
1	G. 2224	39	M	Equal	0	0	Slight	0	0	0	0
2	G. 2356	35	M	,,	0	0	0	0	+	0	0
3	G. 2413	55	M	,,	+	0	0	0	0	0	0
4	H. 14.12.6	18	F	1·2:1	+	0	?	?+	0	+	Coarctation
5	H. 14.14.1	24	M	Equal	0	0	Slight	0	0	0	0
6	H. 14.18.9	41	F	1·2:1	+	+	Slight	+	0	+	Fallot's tetralogy
7	H. 14.18.11	65	F	Equal	+	+	?	+	0	+	Coarctation† Duplication mitral valve
8	H. 14.34.9	55	F	,,	+	0	?	+	+	0	Bicuspid pulmonary valve
9	L. 49	56	F	,,	+	+	0	+	+	+	0
10	L. 84	31	M	,,	+	0	0	0	0	0	Minute third cusp. Syphilitic aortitis
11	L. 117	64	M	,,	+	+	0	0	0	0	0
12	S. C.15.2	45	M	,,	+	+	0	+	0	+	0
13	B. E.17	21	M	,,	0	0	?	?	0	0	Coarctation. Defect in mitral valve
14	B. E.99	39	M	,,	+	0	0	0	+	0	‡
15	B. E.133	57	M	,,	+	+	0	+	0	+	0
16	M. 13.33.14	41	M	,,	0	0	Slight	0	+	0	0
17	M. 14.14.2	70	M	1·2:1	+	+	0	+	0	+	Cystic kidneys and liver
18	T. 1A.1.17	1	M	1·4:1	0	0	+	0	0	0	Biscuspid pulmonary valve
19	T. 1A.1.28	60	M	Equal	+	+	0	0	0	+	Minute third cusp
20	T. 1A.1.29	73	M	,,	+	+	0	+	0	+	0
21	T. 1A.5.3	40	M	,,	0	0	0	0	+	0	0
22	T. 1A.5.7	41	M	,,	0	0	0	0	+	0	0
23	T. S.36309*	65	M	,,	+	+	0	0	0	+	0
24	U. F. 15	23	M	,,	+	0	0	0	0	0	0
25	U.D. 30/53	73	M	,,	+	+	0	0	0	+	0
26	U.D. 166/53	64	F	,,	+	+	Slight	+	0	+	0
27	U.D. 99/54	65	M	,,	+	+	0	0	0	+	0
28	W. H.0178	14	M	,,	0	0	Slight	0	0	0	Coarctation

B.: St. Bartholomew's Hospital. G.: Guy's Hospital. H.: Hammersmith Hospital. L.: London Hospital. M.: St. Mary's Hospital. S.: Royal College of Surgeons. T.: St. Thomas's Hospital. U.: University College Hospital. U.D.: University College Hospital, Dr. Drury's collection. W.: Westminster Hospital.

* St. Stephen's Hospital specimen reported by Smith and Matthews (1955).

† Case reported by Wigle (1957).

‡ Previously reported in *Trans. path. Soc. Lond.* (1897), **18**, 42.

Results

The results are listed in Table II. Of the 28 specimens, 22 were from male and six from female subjects. Of the 24 specimens with cusps of equal size, six had an accompanying congenital abnormality of the heart or aorta. These abnormalities were coarctation of the aorta (three cases, including one specimen which also showed duplication of the mitral valve, and which has been previously described by Wigle (1957)), bicuspid pulmonary valve, and two specimens with a minute third aortic cusp. One of the last-mentioned specimens was originally described by Dr. Peacock, and a drawing of this specimen (19) was

published by Smith and Matthews (1955). Of the four specimens with cusps of unequal size which were included because there was an accompanying congenital abnormality, one had a coarctation of the aorta, one Fallot's tetralogy, and one a bicuspid pulmonary valve; in the fourth the patient had cystic kidneys and a cystic liver. The age distribution of the subjects who had an accompanying congenital abnormality is shown in Fig. 2. There was a definite ridge on one cusp in one specimen (Plate 36, Fig. 5) from an infant, with cusps of unequal size, included because there was in addition a bicuspid pulmonary valve. A further six specimens had an incomplete ridge which did not extend to the free margin of the cusp; five of these had cusps of equal size. In three specimens it was impossible to be certain from inspection whether or not there was a ridge. Three of the specimens with a ridge had an accompanying congenital abnormality. One specimen with unequal-sized cusps had no ridge.

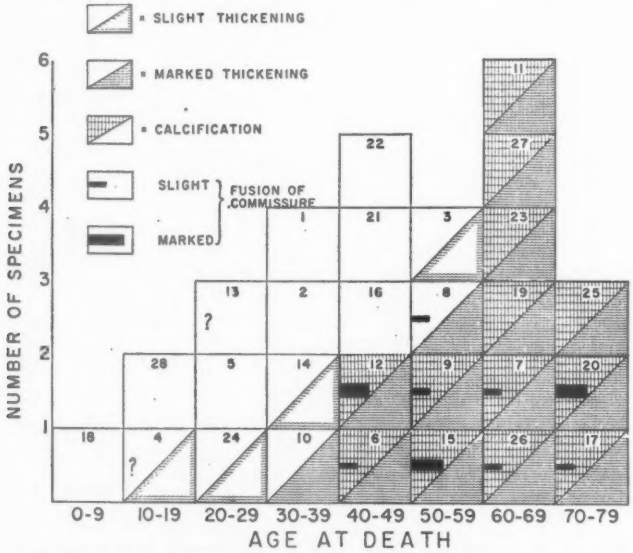

FIG. 1. Changes in bicuspid aortic valves with age (subacute bacterial endocarditis excluded). Each square represents one specimen. The number in the square refers to the specimen number in Table II. Note the increase in incidence of thickening and calcification with age. Fusion of the commissure is infrequent.

An example of a young bicuspid aortic valve (18) is shown in Fig. 5 (Plate 36). It shows the relatively thin cusps which were usual in the younger specimens, though even here there is some nodularity of the cusps, and a small tag on one of them. Fig. 6 (Plate 36) is from a man aged 39 (1). There is thickening and nodularity of the cusps, and a tag on the cusp which has a ridge, but there is no fusion of the cusps. Fig. 7*a* (Plate 37) shows advanced thickening and calcification in a specimen from a man aged 45 (12), and Figs. 7*b* (Plate 37) and 7*c* (Plate 38) are further examples of bicuspid calcific aortic stenosis from two specimens from outside these museums, shown because, being fresh, they were more

easily photographed. Photographs of specimens 19 and 23, both of them examples of bicuspid calcific aortic stenosis, have been previously published (Smith and Matthews, 1955). Fig. 8 (Plate 38; U. B.26A), a specimen rejected because of inequality of the cusps, shows that the thickening and calcification are not necessarily advanced even at the age of 66. Thickening of the cusps was universal beyond the age of 50, but only one specimen from a patient aged less than 20 years at the time of death showed thickening; this specimen also showed coarctation of the aorta. Calcification of the cusps was not seen in

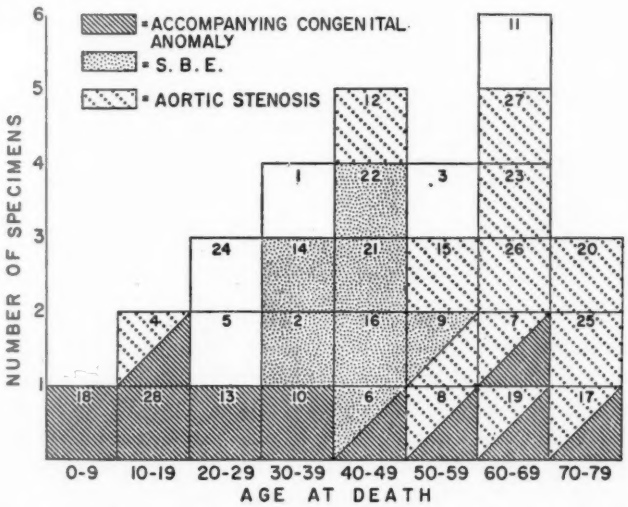

FIG. 2. Incidence of other congenital anomalies, subacute bacterial endocarditis (S.B.E.), and aortic stenosis among bicuspid aortic valves. Note that aortic stenosis is almost universal beyond the age of 50.

specimens from patients whose age was less than 40. The youngest example with a calcified valve was from a woman aged 41 (6) who also had Fallot's tetralogy. The two oldest subjects without calcification of the valve, one man and one woman, were aged 55 (3, 8); beyond this age calcification of the valve was found in all nine specimens. The distribution of calcification is shown in Fig. 1. This process of thickening and calcification can cause aortic stenosis without any fusion of the commissures. Specimen No. 19, for instance, is recorded as having the typical evidence of aortic stenosis in life, and there was obvious left ventricular hypertrophy, yet at autopsy there was no fusion of the two cusps. Of the nine specimens from patients aged more than 60, only four had fusion of a commissure, yet all but one had aortic stenosis, and were in the museums as examples of aortic stenosis rather than bicuspid aortic valves.

Fig. 2 shows the incidence in the series of accompanying malformations, subacute bacterial endocarditis, and aortic stenosis. Subacute bacterial endocarditis was confined to the 30–59 age group. Aortic stenosis occurred

before the age of 40 in only one patient (4), and this patient also had a coarctation of the aorta (Smith and Matthews, 1955, Table I, Case 26). Beyond the age of 60 stenosis was found in all except one specimen (11), which showed thickening and calcification of the cusps, but appeared not to have stenosis.

In these museums a total of 80 specimens of various types of aortic stenosis were found (see Table III). Among them there were 18 examples of bicuspid aortic valvular stenosis with cusps of about equal size, and two of these had minor abnormalities of the mitral valve. We found no example of mitral stenosis combined with bicuspid aortic valvular stenosis. Of the 50 examples of aortic stenosis with three cusps, there were 20 with mitral stenosis in addition.

TABLE III

Description of Aortic Valve in Specimens of Aortic Stenosis in Nine Pathological Museums of London

Tricuspid, without accompanying mitral stenosis	30
Tricuspid, with accompanying mitral stenosis	20
Bicuspid, with cusps of approximately equal size	18
Uncertain	10
Congenital diaphragm	2
Total	80

The association between congenital bicuspid aortic valves and syphilitic aortitis has been recorded by Friedberg and Sohval (1939), Koletsky (1941*a*), Richter (1936), Tranchesi, Carral, de Amorin, and Penaloza (1954), and Wauchope (1928; Cases 24 and 34). We found three examples of this association: H. 14.372.1, rejected because of inequality of the cusps, M. 13.372.1, from a 'pregnant female', not included as the age was not given, and No. 10 (Table II). One example of calcific bicuspid aortic stenosis, with equal cusps, combined with a congenital aneurysm of the sinus of Valsalva (T. 1A.1.30) had no record of the patient's age and sex. One example of bicuspid aortic stenosis was from a patient who had died three months after aortic valvotomy; in this specimen the mitral valve was normal, and there was no history of rheumatism, but the anterior aortic cusp was significantly the larger, and it was excluded from the final series for this reason. No microscopic study had been made (G. 1954/226). The first specimen historically was from St. Bartholomew's Hospital (E. 134) from the collection of 1831–46. This was a good example of calcific bicuspid aortic stenosis, but there were no details of age or sex, and it was therefore excluded. Of the specimens rejected because of a history of rheumatic fever, one also had a coarctation of the aorta (W. 01771), and another had two equal cusps without a ridge (W. 04312). Of those rejected because of inequality of the aortic cusps, and showing no accompanying malformation, three had no ridge on either cusp (S. 15.3; T. 1A.1.6; W. 04312). Neither of the two rejected because of an abnormality of the mitral valve had significant mitral stenosis (H. 14.34.11 had fusion of the cusps for about 5 mm., and L. 48 slight thickening of the cusps). Though excluded, it is likely that five at least of these seven bicuspid valves were also congenital.

Discussion

Incidence of bicuspid valves. Congenital bicuspid aortic valve is probably the commonest malformation of the heart (Lewis and Grant, 1923; Koletsky, 1941*a*), but the reported incidence varies widely. The combined incidence from authors on the subject (de Vries (1918) quoted by Wauchope, 1928; Lewis and Grant, 1923; Wauchope, 1928, Grant, Wood, and Jones, 1928; Bishop and Trubek, 1936; Gross, 1937; Koletsky, 1941*a*) is 0·54 per cent. in a total of 28,431 autopsies, which agrees well with the conclusion of Lewis (1946) that

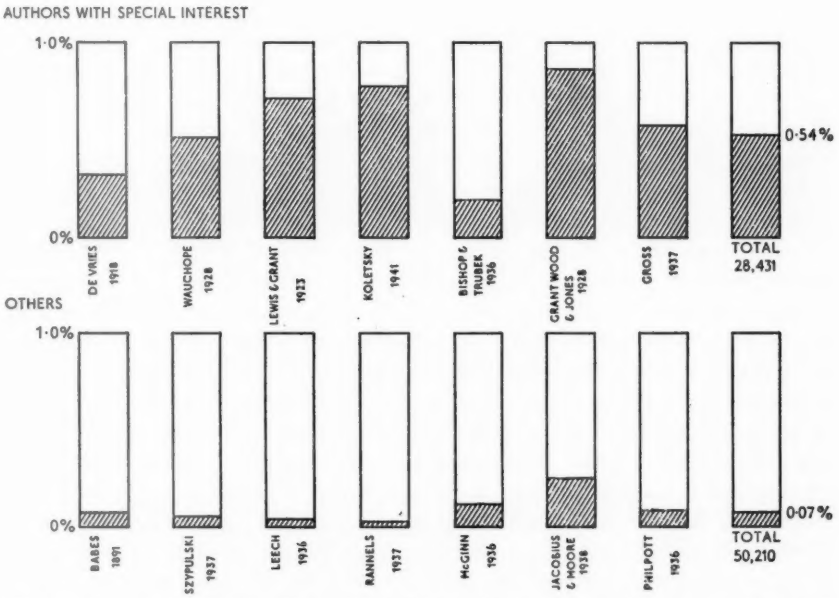

FIG. 3. Reported incidence of bicuspid aortic valves at autopsy. The upper row is taken from authors who have published papers about bicuspid aortic valves. The statistics in the lower row are from authors who have published statistics about the incidence of various forms of congenital heart disease, but have not published a paper about bicuspid aortic valves.

congenital bicuspid aortic valve 'is a very common defect, being found once in every 100 or 200 autopsies'. Figures as to the incidence of the different forms of congenital heart disease, extracted from seven authors, none of whom have published papers about congenital bicuspid aortic valves, show an incidence of 0·07 per cent. in 50,210 autopsies (Fig. 3). These results imply that those who are specifically looking for this lesion find it about eight times as frequently as those who are not. Edwards, Christensen, Clagett, and McDonald (1948) made the comment that, since Abbott (1928) drew attention to the association between bicuspid aortic valves and coarctation of the aorta, the incidence of bicuspid valves had risen with each subsequent review of coarctation.

The figures which they quoted are: Abbott (1928) 23·5 per cent.; Benkwitz and Hunter (1937) 25·3 per cent.; Lewis (1945) 37·5 per cent.; and Reifenstein, Levine, and Gross (1947) 42·7 per cent. In his personal series of autopsies at the Mayo Clinic Edwards (personal communication) found bicuspid aortic valves in 80 per cent. of cases of coarctation. The increasing incidence is more likely to be due to a change in observation than to a change in the disease.

Congenital or acquired? Of the 24 specimens in the present series with cusps of equal size, there was an associated abnormality of the heart or aorta in six. This association is taken as strong evidence that the bicuspid valve is also congenital. (One example of a coarctation, with a bicuspid aortic valve which was judged to be acquired according to the criteria of Lewis and Grant (1923), has been reported (Bishop and Trubek, 1936).) The commonest accompanying malformation is coarctation of the aorta, but bicuspid pulmonary valve has been reported many times (Osler, 1886; Abbott, 1932; Wauchope, 1928; and Koletsky, 1941*a*, who found no less than six bicuspid pulmonary valves in 18 specimens showing bicuspid aortic valves). Where the two cusps are of equal size this is also strong evidence that the lesion is congenital, especially if there is no ridge on either of them to suggest that there has been fusion. There were 16 such specimens in the present series. Karsner and Koletsky (1947) have shown, however, that there may be evidence of a ridge only on microscopic examination when calcification is severe. It is important to recognize also that a ridge may be congenital rather than due to fusion of two cusps. A ridge was present in one cusp of a bicuspid aortic valve from a foetus at seven months' gestation (Osler, 1886), and in 13 of 33 cases, from children less than five years of age, collected by Lewis and Grant (1923). Abbott (1928) reported such a ridge in 23 of 50 bicuspid valves associated with coarctation of the aorta. The incidence of a ridge in our own series is much lower than in most, probably because of the number of specimens in which such a ridge could have been obscured by calcification. The microscopic criteria for making the distinction between a congenital and an acquired ridge were described by Lewis and Grant (1923) and rest mainly on differences in the architecture of the ridge or raphe. Bishop and Trubek (1936) and Koletsky (1941*a*) accepted the conclusions of Lewis and Grant (1923), and amplified them. Even with microscopic examination, however, this separation may be difficult (Abbott, 1932; Gelfman and Levine, 1942), especially when there is advanced calcification (Bishop and Trubek, 1936). Since Lewis and Grant's paper there have been wide differences in the reported incidence of the congenital bicuspid state in different series of bicuspid valves, varying from nine per cent. to 85 per cent. (Fig. 4). It is probable that these differences are due to histological interpretation. This factor is illustrated by the differing conclusions of one author. Koletsky (1941*a*) considered that 69 per cent. of examples (18 of 26) were congenital, and two years later he found 20 per cent. were congenital (10 of 50). By 1947 (Karsner and Koletsky), in cases of calcific aortic valve disease only, this proportion had dropped to nine per cent. (two of 23). Those who concluded that the bicuspid state was much more frequently acquired than congenital (Gross,

1937, Karsner and Koletsky, 1947) did so largely on histological evidence found elsewhere in the heart. Their criteria (Gross, Antopol, and Sacks, 1930), derived from extensive descriptions of the stigmata of chronic rheumatic heart disease other than the Aschoff node, are open to doubt. Using the same criteria, Hall and Anderson (1943) examined 112 hearts without valvular lesions 'as commonly understood', and found such rheumatic stigmata in 90 per cent. Pathologists tend to use the same criteria whatever the age of the specimen. It is particularly doubtful whether microscopic evidence of inflammation in

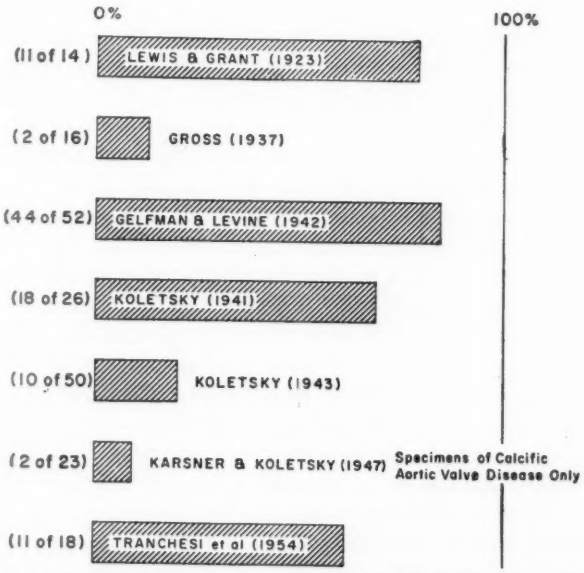

FIG. 4. Bicuspid aortic valves; reported incidence of congenital malformations. The cross-hatched rectangles represent the proportion of specimens of bicuspid aortic valves which were considered by the respective authors to be congenital rather than acquired.

bicuspid aortic valves can be used as an argument that the bicuspid state is the result of chronic rheumatic heart disease. Congenital bicuspid valves, being malformed, are probably prone to abnormal stress, and there is support for this contention in the findings of Grant, Wood, and Jones (1928), which are discussed later. By the age of 60 the abnormal cusps have come together with a forceful blow at least 2,500 million times, and it would be surprising if there were no residual effect to be detected microscopically.

Cusp size. Considerable discrepancy in the size of the two cusps is compatible with a congenital lesion (Lewis and Grant, 1923; Koletsky, 1941*a*). Koletsky found exactly equal cusps in only two of his 18 specimens, and accepted a difference as large as one cusp of 4·5 cm. and the other of 2·5 cm. as a congenital abnormality. Can a bicuspid aortic valve with cusps of approximately equal

size occur as an acquired lesion? None of our specimens showed any evidence of rheumatic affection of the mitral valve, even when there was aortic stenosis. Koletsky (1943) has suggested that such congenitally abnormal aortic valves are peculiarly liable to rheumatic disease, and if this is so it is surprising that the mitral valve should be spared. Theoretically it is possible that rheumatism might cause the fusion of two cusps during the growing period, and that subsequently the single cusp might grow to equal the conjoined cusp in size. The only published reference that we can find to mitral stenosis in association with a bicuspid aortic valve with equal-sized cusps is in a footnote (Gross, 1937). In two specimens of our series there was a diminutive third cusp. Semantic considerations hardly permit these valves to be labelled as bicuspid, yet such examples can be considered as undoubted malformations, and when there is aortic stenosis, as in No. 19, it can be regarded with confidence as having arisen on a malformation. The latter example also shows that malformation of the aortic valve other than the pure bicuspid state may lead to aortic stenosis in later life, and suggests that this fact may have wider implications.

Sex. In our 28 specimens the sex difference, 22 male (79 per cent.) and six female (21 per cent.), is similar to that which is usually found in congenital bicuspid aortic valves. Of the 83 cases collected by Lewis and Grant (1923) in which the sex was recorded, 63 (76 per cent.) were from male and 20 (24 per cent.) from female subjects. Wauchope (1928) collected 52 cases, of which 42 (81 per cent.) were from male subjects, from the post-mortem records of the London Hospital. Thirteen (76 per cent.) of 17 in Koletsky's (1941*a*) series were from male subjects; in one the sex was not known. It is of interest that seven of the eight specimens considered, on histological evidence, to be examples of acquired bicuspid aortic valves by the same author (Koletsky, 1941*b*) were also from male subjects. In only one of the eight was there a history of rheumatic fever; in this specimen the two aortic cusps were unequal, and it was the only one with mitral stenosis. Perhaps the majority, with this one definite exception, were also specimens of congenital rather than acquired bicuspid aortic valves. It is unusual for rheumatism to affect male subjects predominantly, and the aortic valve without the mitral. As with the congenital variety of malformation, the coronary cusps in Koletsky's examples were the ones most frequently conjoined, a fact also noted in the case of acquired bicuspid valves by Lewis and Grant (1923). The similarity between the congenital and the supposedly acquired lesions in these respects raises some doubts about the validity of the histological criteria used to separate them.

Ageing processes

1. *In tricuspid aortic valves.* There is growing awareness of the fact that normal aortic valves undergo progressive sclerosis with age. Mönckeberg (1904) considered that calcification of the aortic valve was almost physiological after the age of 35. Hultgren (1948) in 100 unselected post-mortem examinations, found radiographically that 46 showed calcium deposits in the aortic valve or ring. No such deposits were found in patients under the age of 40, but they

occurred in the majority of those over 60 and in all those aged more than 80. There was evidence that male subjects were more liable to calcification of the valve. McGinn and White (1934), Sohval and Gross (1936), and Pyke and Symons (1951) came to similar conclusions. Hypertension, by increasing the trauma of valve closure, may also predispose to such changes in the valve, as it does in the aorta (Magarey, 1956), and this may explain why the stenotic aortic valve has a far greater liability to calcification than the stenotic pulmonary valve (Campbell and Kauntze, 1953); in the latter calcification is rare, but occasionally occurs in old age (Barritt, 1954). Disorders of calcium metabolism (Libman, 1940), xanthomatosis (Boas, Elster, and Adlersberg, 1954), and Paget's disease (Hultgren and Caul, 1958) may hasten the process. The pathological changes are reminiscent of those which are found in atheroma; they are commoner in male subjects, and progress from lipid deposition to calcification. When they occur in women there is an abnormal incidence of hypercholesterolaemia (Boas, Elster, and Adlersberg, 1954).

The evidence in favour of aortic stenosis resulting from such a pathological process has been frequently reviewed, and is still widely accepted despite numerous attempts to prove that aortic stenosis is almost invariably rheumatic (for example, Karsner and Koletsky, 1947). In elderly patients with isolated aortic stenosis a history of rheumatism is rare (Mitchell, Sackett, Hunzicker, and Levine, 1954), especially in men (Matthews, Medd, and Gorlin, 1955), though Christian (1931) attributed this rarity to poor memory and the long interval since the suspected attack. In the face of this evidence it is surprising to see that in Wartman and Hill's (1953) textbook only one and a half pages are devoted to changes in the heart due to age, and that most of this space is given to a quotation from Karsner (1940), whose argument is that changes in the valves cannot be attributed to ageing. There appear, on the contrary, to be such changes, though, as with atheroma, the connection may be indirect. If degenerative or Mönckeberg's sclerosis is accepted, then the opposite interpretation to that which the authors intended may be put upon the statement that 'if the Mönckeberg type of sclerosis exists, this study suggests that it cannot be distinguished morphologically from that associated with rheumatic fever, chronic or extinct' (Karsner and Koletsky, 1947). In the clinical field, degenerative sclerosis as a cause of aortic stenosis best explains the observation of Bruns and van der Hauwaert (1958) of the increasing incidence of aortic systolic murmurs with age. The widely accepted fact, that isolated calcific aortic stenosis is compatible with a normal life span, is more easily understood if the obstruction to blood-flow is caused by a degenerative process in the last years before death, rather than by a long-standing rheumatic stenosis of the valve. Mention has already been made of the unreliability of the pathological criteria for diagnosing rheumatic heart disease. Christian (1931) and Mitchell, Sackett, Hunzicker, and Levine (1954) have emphasized the belief that pathologists were under pressure from clinicians in coming to the view that calcific aortic stenosis was nearly always a manifestation of rheumatic heart disease.

2. *In bicuspid aortic valves.* Paget (1844) was the first to draw attention to

the fact that congenital bicuspid aortic valves had a peculiar liability to disease, but their importance as something other than a pathological curiosity was not established until Osler (1886) described their abnormal liability to subacute bacterial endocarditis. Peacock (1858) pointed out that they may become the seat of chronic inflammation 'by which they are rendered thick and unyielding and often become extensively ossified, thus inducing, first obstruction to the flow of blood from the ventricle into the aorta, and then incompetency'. Grant, Wood, and Jones (1928) and Grant (1936) provided an acceptable explanation for these two fates of the bicuspid aortic valve. They found non-bacterial fibrin vegetations in 2 per cent. of normal mitral valves, in 50 per cent. of rheumatic mitral valves (and similar vegetations on the rheumatic aortic, tricuspid and pulmonary valve, in order of decreasing incidence), and also in six of 12 congenital bicuspid aortic valves. The vegetations are nearly always situated on or about the lines of closure of the cusps, indicating that they are caused by the mechanical factor of the impact of opposing cusps. The underlying fibrous tissue shows degenerative changes. The authors stressed the special liability of these valves to flattened fibrous patches (Lambl's excrescences); and Magarey (1949) considered that these patches result from organization of the fibrin thrombi. These fibrin thrombi predispose to bacterial invasion (Grant, Wood, and Jones, 1928; Keefer, 1940), but, if they escape infection, organization leads to a gradual sclerotic process in the valve (Grant, Wood, and Jones, 1928). The progress of collagenous degeneration, lipid deposition, and calcification is similar to that which occurs with the passage of time in the aortic valve with three cusps, but perhaps because of the stresses of abnormal closure, the changes occur at an earlier age. If the valve escapes subacute bacterial endocarditis at an earlier age, it is fated to a degenerative process and to calcification by the age of 50 or 60. Aortic stenosis may result from thickening and calcification of the cusps, generally without fusion of the commissures. Bicuspid aortic valves of normal thickness in old age were not found in our search of the museums, and discussion with many pathologists suggests that they seldom occur.

Bicuspid aortic stenosis. It is a curious fact that, though the liability of the bicuspid aortic valve to subacute bacterial endocarditis has been generally recognized since it was described by Osler in 1886, the liability to calcific aortic stenosis seems largely to have been overlooked in spite of its clear description by Thomas Peacock in his textbook 28 years before. Several illustrations of bicuspid calcific aortic stenosis with cusps of equal size have been published (Lewis and Grant (1923) Fig. 16; Abbott (1932) Fig. 6; Bishop and Trubek (1936) Figs. 4, 5, and 9; Gross (1937) Fig. 1; Hall and Ichioka (1940) Fig. 4; Karsner and Koletsky (1947) Fig. 7 (though they regarded this as an example of an acquired bicuspid valve); Campbell and Kauntze (1953) Fig. 11).

Reference has previously been made to authors who have described the liability of the congenital bicuspid aortic valve to develop aortic stenosis (Smith and Matthews, 1955), the highest estimate, from the Massachusetts General Hospital, being that 80 per cent. of cases of calcareous aortic stenosis

develop on this basis (Mallory, 1947). At the same hospital 20 to 30 per cent. is now thought to be a more probable figure (Dr. B. Castleman, personal communication). When aortic stenosis arises in a bicuspid aortic valve, it can do so from rigidity and calcification of the cusps (for example, Nos. 19, 23, 25, 26, and 27) without fusion at the commissures. From the data of Lewis and Grant (1923), Gelfman and Levine (1942), Koletsky (1941*a*, *b*), and Tranchesi, Carral, de Amorin, and Penaloza (1954), it appears that about 75 per cent. of all bicuspid aortic valves encountered *post mortem* are congenital (Fig. 4), and if the cusps are approximately equal in size the proportion is probably much greater. It has become usual, however, when there is calcific aortic stenosis, to assume that the bicuspid state is acquired, even when the cusps are of equal size, particularly since Karsner and Koletsky (1947) concluded that, of their 200 specimens of calcific aortic stenosis, only four failed to show what they regarded as histological evidence of chronic rheumatic heart disease. If the aortic cusps are approximately equal in size, the burden of proof should be on the pathologist to show that the lesion is rheumatic, because, from the figures quoted above, the majority of such specimens are probably congenital. In the confusion which appears to prevail as to what are the pathognomic histological criteria of rheumatic heart disease, there is reason in Grant's (1936) view that without finding Aschoff nodes certainty is impossible, and even this criterion has been questioned (Hall and Anderson, 1943). It is, however, true of rheumatic heart disease in general that Aschoff nodes are found with decreasing frequency with age, and that in old age they are extremely rare (Coombs, 1924). The data here quoted do not permit an estimate of the frequency of degeneration in a bicuspid aortic valve as a cause of calcific aortic stenosis. There were, however, more examples of aortic stenosis than there were of subacute bacterial endocarditis, which suggests that bicuspid valves may be at least as liable to develop aortic stenosis as they are to become infected. Hall and Ichioka (1940) found eight, and possibly nine, examples of bicuspid valves in 19 specimens of isolated aortic stenosis, and no bicuspid aortic valves in 12 specimens of aortic stenosis in which the mitral valve was also affected. Karsner and Koletsky (1947) had 23 bicuspid aortic valves in their series of 200 specimens of calcific aortic valve disease, and 16 of these had no gross evidence of disease of the other valves. Their own conclusion, that 21 of the 23 had evidence of rheumatic heart disease, is open to doubt for the reasons given. Taking all these results together, it can be suggested that perhaps 5 to 10 per cent. of all cases of isolated calcific aortic stenosis arise from degeneration in malformed aortic cusps; this proportion is probably higher, and may be much higher, in patients aged more than 50.

At the present time there is no way of diagnosing the bicuspid state of the aortic valve in life. Herrick (1933) and Levine and Harvey (1949) have observed that some patients who have no more than a quiet basal systolic murmur in middle age may develop the full picture of aortic stenosis in old age. In some of these patients it is possible that the basal murmur was due to a bicuspid valve, and the aortic stenosis to its subsequent sclerosis. The specimen shown in Fig. 7*b* (Plate 37) may be an example of this course of events. Referring to the

development of aortic stenosis on bicuspid aortic valves, Bailey, Bolton, Jamison, and Nichols (1954) concluded: 'This is not an academic question, since the presence or absence of commissural fusion, so characteristic of rheumatic aortic stenosis, is the most important single element determining the type and effectiveness of possible corrective valve surgery.' When aortic stenosis results from rigidity of the cusps alone, as was the case in four of the 13 examples of aortic stenosis in this present series, or when fusion is only slight, as was the case in the remainder, valvotomy can increase the size of the orifice significantly only if a cusp is split.

It is appreciated that a study of museum specimens has many disadvantages, and these conclusions are put forward as a preliminary to a study of fresh specimens of bicuspid aortic valves and of aortic valvular stenosis.

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Summary

Bicuspid aortic valves were examined in nine of the pathological museums of London. From 55 such specimens a series of 28 was selected because they were almost certainly congenital, though many of the remainder were probably also congenital.

Twenty-two of the 28 were from male subjects. Ten had a coexisting congenital anomaly. Thickening of the valve cusps increased with age. Calcification appeared in the fifth decade, and was found in all the nine specimens from patients aged more than 60 at the time of death. Seven specimens showed bacterial endocarditis, and in no less than 13 there was aortic stenosis which was calcific in all but one case. Valve rigidity, rather than fusion of the cusps, was then the major determinant of obstruction to blood-flow.

These findings support Peacock's (1858) suggestion that malformed valves may lead by a degenerative process to aortic stenosis. Twenty-eight years later Osler drew attention to their liability to subacute bacterial endocarditis. It is suggested that a congenital bicuspid aortic valve is liable to develop calcific

degeneration earlier and more consistently than a normal valve, and that these changes may lead to aortic stenosis. Though less widely recognized, this may indeed be a commoner fate than the development of subacute bacterial endocarditis, and may be responsible for a significant proportion of cases of isolated calcific aortic stenosis in elderly subjects. It is emphasized that congenital bicuspid aortic valves are by far the commonest valvular malformation of the heart, and that they may be even commoner than is at present realized, because when they have undergone calcific degeneration they may go unrecognized.

Of 80 specimens of aortic valvular stenosis in these museums, 18 were bicuspid. None of the 18 had accompanying mitral stenosis, although two had minor abnormalities of the mitral valve. Of 50 examples of three-cusped aortic valvular stenosis, no less than 20 had mitral stenosis in addition. These findings support the contention that bicuspid aortic valvular stenosis is a degenerative rather than a rheumatic process. It is suggested that this possibility has been overlooked partly because of the uncertainty of the pathological criteria for diagnosing chronic rheumatic heart disease, partly because of the difficulty in using such valid criteria as there are when there is advanced calcification, and partly because it is not widely appreciated that congenital bicuspid aortic valves may be unequal in size, and that when one cusp has a ridge this does not necessarily indicate fusion of two cusps at that site.

These examples of calcific bicuspid aortic stenosis are also proposed as additional evidence that calcific aortic stenosis occurring in old age is, in the majority of cases, the result of a degenerative rather than a rheumatic process. It is widely accepted that death may occur from calcific aortic stenosis in extreme old age, and even at this age it may be an incidental post-mortem finding. This is perhaps best explained on the basis that obstruction to blood-flow is often present for a relatively short time before death.

These findings require confirmation from fresh specimens with good clinical records. The question is not entirely an academic one, for it bears on the likely effectiveness of valvotomy.

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FIG. 5. Specimen No. 18 (Table II). A boy aged one year. Note unequal cusps and well-marked ridge. Specimen included because of coexisting bicuspid pulmonary valve. (St. Thomas's Hospital 1A.1.17)

FIG. 6. Specimen No. 1 (Table II). A man aged 39. (Guy's Hospital 2224)

FIG. 7*a*. Specimen No. 12 (Table II). A man aged 45. (Royal College of Surgeons C.15.2.) Note the advanced calcific degeneration and approximately equal size of the cusps

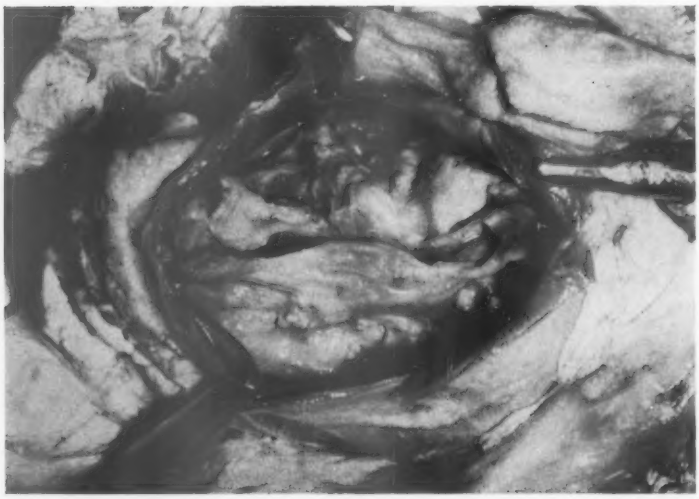

FIG. 7*b*. A specimen sent to St. Thomas's Hospital by Mr. Mason of Newcastle. The patient was stated to have had a 'small murmur' in 1918, but he was free of symptoms until the age of 52, when he developed dyspnoea on exertion, anginal pain, and latterly, cardiac failure with typical signs of aortic stenosis. Death occurred during an operation on the aortic valve. The two cusps are seen to be equal in size, heavily calcified, and rigid, and one commissure is fused for 5 mm. The mitral valve was macrospically normal, and there was no history of rheumatism

FIG. 7c. Calcified bicuspid aortic stenosis from a patient (Mrs. C. A., aged 73) with typical signs of aortic stenosis. The mitral valve orifice was normal, but there was some fusion of the chordae tendineae. There was no history of rheumatism. A specimen supplied through the kindness of Dr. E. B. French and Dr. A. J. M. Drennan of Edinburgh

FIG. 8. A woman aged 66. Not included in the series because of inequality of the cusps. (U.C. Hospital B.26.A)

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KLINEFELTER'S SYNDROME[1]

Clinical and Hormonal Aspects

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With Plate 39

THE great majority of cases of male hypogonadism can be separated clearly into two major classes (Mack, 1952): those due to pituitary failure, and those in which the fault lies primarily in the testis itself. The most important member of the latter group is Klinefelter's syndrome. As the importance of this syndrome has been more generally recognized, and the number of cases with some claim to be included within it has increased, it has unfortunately become increasingly difficult to define it exactly, or to say with certainty how many sub-groups are comprised within it. The historical approach may help to clarify the present position and, at the same time, serve to emphasize the need for caution in classifying cases of male hypogonadism. Indeed, it is our belief that a too willing acceptance of the various schemes already put forward has resulted merely in increasing confusion as fresh facts are discovered. The patients originally described by Klinefelter, Reifenstein, and Albright (1942) were masculine in appearance, but showed gynaecomastia. Their testicles were small, and histologically the Leydig cells were greatly increased in number, while the seminal tubules were degenerate and hyalinized. The seminal fluid contained no sperms, and excretion of follicle-stimulating hormone was increased. Heller and Nelson (1945) under the name of 'puberal seminiferous tubule failure' extended this concept to include patients without gynaecomastia who might, however, be mildly or grossly eunuchoid. Howard, Sniffen, Simmons, and Albright (1950) followed the lead of Heller and Nelson with reservations. They described a series of cases under the term 'sclerosing tubular degeneration': this series included the original patients of Klinefelter along with further subjects who showed evidence of eunuchoidism, varying from mere lack of hairiness of the chest and abdomen to gross bodily changes, though the authors pointed out that the degree of eunuchoidism was not so marked as in typical cases with a low level of excretion of follicle-stimulating hormone. The testicular picture was similar to that already described, but it was noted that a few tubules might show attempts at spermatogenesis. The same authors excluded

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the del Castillo syndrome—'absence of germ cells'—from the 'sclerosing tubular degeneration' group, but they mentioned that one patient with the former syndrome had large breasts, most had small testes, and excretion of follicle-stimulating hormone was, on the whole, increased.

Fresh interest was aroused by the discovery (Plunkett and Barr, 1956) that some, but not all, of these patients are chromatin-positive by the method of nuclear sexing: that is, they are presumptive genetic females bearing the XX chromosome pair, and show complete sex reversal. All experience, including our own (Ferguson-Smith, Lennox, Mack, and Stewart, 1957, 1959; Ferguson-Smith, 1958; Stewart, Ferguson-Smith, Lennox, and Mack, 1958) goes to show that the chromatin-positive group forms a homogeneous entity, whose pathogenesis presents many fascinating problems which, however, do not concern us here (see for example, Grumbach, Blanc, and Engle, 1957; Segal and Nelson, 1957; Witschi, Nelson, and Segal, 1957; Ferguson-Smith, Lennox Mack, and Stewart, 1959; and several contributions to the Symposium on Nuclear Sex, 1958). The problem of classifying patients who hitherto had been regarded as being examples of Klinefelter's syndrome, but were discovered to be chromatin-negative, has been approached in very different ways by various authorities. Some (Nelson, 1957) have discarded this group completely, or have labelled it as 'false' Klinefelter's syndrome. Others, having admitted a few chromatin-negative cases to their series, have arrived at the conclusion that chromatin-positive cases are far more numerous. Neither of these attitudes is justifiable in our experience. Clinically and hormonally the two groups resemble and shade into each other. Histologically they are distinct, but even there some of the chromatin-negative cases display a picture closely similar to the chromatin-positive ones. As a group of workers, our views have altered several times, and individually we have never been unanimous upon all points of differentiation. We have published elsewhere (Ferguson-Smith, Lennox, Mack, and Stewart, 1957) our views on testicular histology. In the present contribution are presented the results of a mainly clinical approach, taking groups of cases of chromatin-positive and chromatin-negative Klinefelter's syndrome and controls, all reasonably homogeneous in origin and in the mode of their investigation, and endeavouring to determine the nature of any differences between the groups. It must not be thought that, although for the purposes of this study we have deliberately chosen to retain the term chromatin-negative Klinefelter's syndrome, we necessarily believe that the patients so described form a homogeneous group. We strongly suspect that they do not, and that further knowledge will lead to their subdivision; we are reluctant, however, to abandon at this stage a term which we find so useful in describing certain cases of male hypogonadism.

Patients Investigated and Methods

Source and diagnosis of cases and controls. Thirty-two cases of Klinefelter's syndrome are described. Except that, to make up the even numbers, one

chromatin-positive patient has been included who was originally investigated elsewhere, all were patients attending the Urological Department of the Western Infirmary, Glasgow, for investigation of subfertility. The diagnosis was established by the demonstration of sex chromatin in oral mucosal smears (Moore and Barr, 1955) in the chromatin-positive cases. In the chromatin-negative cases the ultimate diagnostic criterion has always been testicular

TABLE I

Grading of Some Clinical Features

1. *Prostate*

Grade	*Estimated size by rectal palpation*
0	Not palpable
1	Less than normal
2	Normal
3	Slight enlargement
4	Moderate enlargement

2. *Gynaecomastia*

Grade	*Clinical estimate*
0	Nil or minimal
1	Slight
2	Moderate
3	Severe

3. *Abdominal hair*

Grade	*Amount of hair on linea alba*
0	Profuse
1	Scanty normal
2	12 hairs or fewer
3	Nil

4. *Facial hair*

Grade	*Amount and site*
0	Profuse all over face
1	Scanty normal, mainly lips and chin
2	Less than normal, only lips and chin
3	Nil

biopsy, our histological criteria having been given in detail elsewhere (Ferguson-Smith, Lennox, Mack, and Stewart, 1959). We include both cases of the classical type described by Nelson and Heller (1945), with Leydig-cell hyperplasia and hyalinization of the seminiferous tubules, and those cases, first described by del Castillo, Trabucco, and de la Balze (1947), in which the predominant feature is a total or near-total disappearance of germ cells from otherwise well-formed Sertoli-cell-lined tubules. Part of the object of the present investigation was to determine whether any clinical difference could be established between those two varieties, or whether we were justified in regarding them as essentially similar. From the same subfertility clinic 16 male subjects with normal sperm counts (40,000,000 sperm per ml. or more), whose wives were apparently subfertile, formed a control group.

Investigations. The clinical history included the results of inquiry con-

cerning previous mumps, testicular trauma, orchitis, jaundice, venereal disease, tuberculosis, testicular maldescent, or herniorrhaphy. In addition the age at which shaving commenced and the frequency of shaving were noted. Detailed clinical examination included a search for evidence of hypogonadism and eunuchoidism, and an estimate of the severity of important signs. The sole-to-pubis measurement, from the floor to the upper border of the symphysis pubis, was made with the patient standing erect. The crown-to-pubis measurement was obtained by subtraction from the standing height. The arm span was measured with the patient facing a wall and stretching as far as possible. By this method (which results in less variation between successive measurements on the same patient than does the usual method) span measurements are on the average about one inch greater than when taken with the patient with his back to the wall, and the span-height difference is consequently slightly increased. The longest axis of each testis was estimated by palpation. (Having frequently had the opportunity of checking such measurements at operation, we find our estimates are accurate to within 2 to 3 mm. at most.) An arbitrary grading of hair distribution on the face and abdomen, of prostate size, and of gynaecomastia, was adopted (Table I).

Hormone estimations were obtained in many cases. Total daily urinary excretion of 17-ketosteroids was measured by the method of Tompsett and Oastler (1946). The normal range for men is 9 to 24 mg. per day. Fractionation into α and β portions was carried out by the method of Haslam and Klyne as described by Varley (1954). In the normal person the α fraction constitutes 81 to 99 per cent. of the total. The 24-hour urinary output of gonadotrophins (follicle-stimulating hormone) was estimated by the method of Loraine and Brown (1956). Hormone estimations were not done in the original control cases, but a series of normal men in the same age group gave values for follicle-stimulating hormone uniformly below 10 mouse units per day. Oestrogens were estimated chemically by the method of Brown (1955). Normal values in men of urinary excretion in μg. per 24 hours are: oestriol, 0·8 to 7·5; oestrone, 3·4 to 8·2; oestradiol, 0 to 2·4.

A radiological skeletal survey was carried out in 10 cases, and included films of skull, sinuses, pelvis, and long bones.

Results

The results are shown for chromatin-positive and chromatin-negative cases in Table II*a*, and for normal controls in Table II*b*. For objective measurements, mean values and estimation of the significance of differences are shown in Table III. Significant findings in the signs graded arbitrarily are given in Table IV. Photographs of our chromatin-positive and chromatin-negative patients (Plate 39) illustrate some of the clinical features. The bone ages of all patients surveyed radiologically (five chromatin-positive and five chromatin-negative) were adult. The sinuses and skulls were normal, and the pelves, which were compared with an equal number of normal controls, were all classified as male.

TABLE IIa

Details of cases of Klinefelter's Syndrome

	Case number	Age (years)	Shaving: Began at age	Shaving: Times per week	Aetiological factors[1]	Measurements (inches): Height	Span	Pubis to sole	Testes (inches): L.	Testes (inches): R.	Arbitrary grading (Table I): Gynaecomastia	Prostate	Face hair	Pubic hair	Sperm count[2]	Follicle-stimulating hormone (mouse units)	17-Ketosteroids (mg./24 hrs.): Total	a	β	Oestrogens (μg./24 hrs.): Oestrone	Oestradiol	Oestriol	Biopsy[3]	Other findings[4]
Chromatin-positive	1	29	16	2	—	69	72	35·5	0·8	0·8	2	3	0	0	0	80	18·6	17·6	1·0	..	..	..	T	—
	2	35	15	7	V	73·5	75·5	38·5	0·8	0·8	0	1	1	1	< 1 M	40–80	18·3	17·4	0·9	1·9	0·3	0·0	T	—
	3	29	20	3·5	M	69	66·5	36	0·6	0·6	0	2	0	0	0	80	19·2	17·3	1·8	..	..	..	T	—
	4	36	17	3·5	—	74·5	75·5	40	0·6	0·6	0	3	0	0	< 1 M	80–160	18·9	16·8	2·1	4·0	0·6	0·0	T	—
	5	29	20	2	—	69·25	72	35	1·0	1·0	1	2	1	1	0	20	22·7	21·9	0·8	6·0	6·0	5·1	T	—
	6	35	17	7	M	67	68·75	36	0·6	0·8	1	1	0	0	0	..	..	..	..	..	..	..	..	—
	7	34	27	< 1	M	67·25	67·75	34	0·6	0·4	1	2	1	1	0	80	9·2	7·8	1·4	..	..	..	T	LI
	8	42	14	2	—	65·5	68	32·5	0·6	0·6	2	1	2	3	1 S	40	15·9	14·8	1·1	3·5	1·2	6·0	T	Br
	9	39	20	1	M	68·5	70	34·5	0·6	0·6	0	1	1	3	..	40–80	11·5	10·5	0·9	..	..	..	..	RC
	25	31	21	1	T	66·75	68	35	0·6	0·6	2	0	1	2	9 S	80	..	..	..	..	..	..	T	LI; Br
	26	26	20	3	M	63·5	64	32·5	1·0	1·0	2	2	1	1	0	40–80	12·9	11·3	1·6	..	..	..	T	LI
	27	27	16	7	M	70·5	72	37	0·8	0·8	1	..	0	0	0	..	..	..	..	..	..	..	T	—
	28	37	19	3·5	T	70·5	70·5	37·5	0·6	0·6	2	1	2	2	..	40–80	..	..	..	..	..	..	T	Br
	29	31	18	7	T	69	72·25	35	0·6	0·6	1	1	1	2	..	..	..	..	..	..	..	..	T	—
	30	33	17	3	H	70·5	72·5	36·5	0·8	0·8	0	2	1	2	..	..	..	..	..	..	..	..	T	LI; RC
	31	29	27	7	M	69·5	74·25	37·5	0·8	1·0	0	0	0	1	0	..	..	..	..	..	..	..	..	—
Chromatin-negative	10	32	22	3	—	69·5	71·25	35	1·2	1·4	0	2	0	1	0	10–20	..	..	..	..	..	..	A	CB
	11	29	22	2	M	65·75	66·5	32·5	1·0	1·0	0	1	1	3	5 S	40–80	12·7	11·8	0·8	..	..	..	A	—
	12	29	18	3	—	66·25	69·5	34·5	1·4	1·4	2	3	1	0	2 S	40	16·2	14·1	2·1	3·6	0·6	3·6	A	—
	13	29	16	3·5	I	64·25	67·75	33	1·6	1·6	0	2	1	1	0	20–40	12·5	11·0	1·5	3·2	0·8	2·8	A	—
	14	31	18	7	H	67·25	69	33·5	1·4	1·4	0	2	0	0	1 S	20–40	..	..	..	..	..	..	F	—
	15	31	16	2	—	68·5	70	34·5	0·8	0·8	1	2	1	2	< 1 M	80–160	12·5	11·8	0·7	3·2	0·0	4·8	F	—
	16	32	..	7	—	66·5	67·5	33	1·2	1·0	0	3	0	0	< 1 M	..	..	..	..	..	..	..	F	—
	17	40	20	7	—	59	59·5	29	0·6	0·6	1	3	0	0	0	40	..	..	..	..	..	..	A	CB
	18	37	16	3	M, T	69	73	35·5	1·2	1·2	0	2	0	0	8 S	20	15·3	14·5	0·8	6·6	1·8	1·2	F	—
	19	31	16	7	M, I	72	75·5	36·5	1·4	1·4	0	2	0	0	6 S	20	11·8	11·1	0·8	..	..	..	F	—
	20	29	16	3	—	62·5	67·5	33	1·6	1·6	0	2	0	1	0	..	..	..	..	..	..	..	A	RC
	21	30	18	3·5	—	68·5	20·25	34·5	0·8	1·2	0	1	1	3	0	80	21·1	18·1	3·0	..	..	..	F	—
	22	38	15	7	H	66·75	68·5	34·5	1·0	—	0	2	0	1	0	80	8·3	7·3	1·0	..	..	..	F	—
	23	39	16	7	—	62	66	31	1·2	1·2	1	3	0	0	2 S	..	..	..	..	..	..	..	F	CB
	32	29	15	7	H	66·5	68·5	33	0·8	1·2	1	4	0	2	10 M	40	..	..	..	..	..	..	F	—
	33	26	15	7	T	68·5	70·5	35	1·4	1·4	0	3	0	3	10 S	80–160	..	..	..	..	..	..	A	—

[1] History of: H, hernia; I, injury; M, mumps; T, tuberculosis; V, venereal disease.
[2] M = million/ml.; S = number of single spermatozoa seen on examination of film.
[3] T = typical chromatin-positive histology; F = 'typical' chromatin-negative histology, with fibrosis of tubules; A = absence of germ cells, without fibrosis.
[4] LI = low intelligence; Br = bronchiectasis or early chronic bronchitis; RC = renal calculus; CB = colour blind.
— Negative finding; .. No observation.

Testicular size. Each of our three groups covers a separate range of sizes, the testes in the chromatin-positive cases being smallest, in the chromatin-negative intermediate, and in the controls largest, with very little overlap. The largest chromatin-positive testis is just over half the size of the smallest control (Table II). Differences of mean sizes are clearly significant (Table III).

Body measurements (Tables II and III). In the chromatin-positive group both the height and the sole-to-pubis measurements are significantly greater than the corresponding measurements either of the chromatin-negative or of the control group. The span and the crown-to-pubis measurements are much

TABLE II*b*

Details of Control Cases

		Shaving			Measurements (inches)			Testes (inches)		Arbitrary gradings (Table I)				
Case number	Age (years)	Began at age	Times per week	Aetiological factors[1]	Height	Span	Pubis to sole	R.	L.	Gynaecomastia	Prostate	Face hair	Pubic hair	Sperm count[2]
A	26	17	7	—	67·25	69·5	34·5	1·8	1·8	0	1	0	0	80 M
B	36	16	7	—	65·75	69·5	33	2·0	2·0	0	1	0	1	110 M
C	42	19	3·5	T	64	69·5	31	2·0	2·0	0	2	0	1	100 M
D	28	20	2	T	67·25	69·5	34·5	2·2	2·2	1	2	1	1	60 M
E	31	19	7	T	63·5	67	31·75	2·0	2·0	0	3	0	0	84 M
F	38	18	3·5	—	67·25	64·5	34	2·2	2·2	1	3	0	0	150 M
G	34	16	7	—	62	65·5	31·5	2·0	2·0	0	2	1	0	140 M
H	30	16	7	—	65·25	69	33·5	2·2	2·2	0	2	0	1	120 M
I	33	18	7	V	69·5	71·75	36	2·0	2·0	0	3	0	0	58 M
J	32	17	4	M	65·25	67	33	2·0	2·0	0	3	0	0	120 M
K	33	18	7	—	67·5	70·5	35	2·0	2·0	0	2	0	0	140 M
L	29	18	2	H, M, T	69·5	73·5	34·5	2·0	2·0	0	2	0	0	120 M
M	31	16	7	M	70	70	35	2·0	2·0	0	3	0	0	125 M
N	27	21	7	I	67·75	71	34·5	2·0	2·0	0	2	1	1	185 M
O	35	17	7	—	66	68	34·5	2·2	2·2	1	3	0	0	80 M
P	35	16	3·5	—	67·5	69	35	1·8	1·8	0	2	0	0	60 M

[1, 2] See notes to Table II*a*

the same in all three groups. No measurements of the chromatin-negative group differ significantly from normal. The one significant divergence is the high sole-to-pubis measurement of the chromatin-positive group. This long-leggedness is solely responsible for the increased height of this group, and produces the effect (an apparent paradox in the presence of eunuchoidism) of a *decreased* span-height difference, rendering the latter measurement positively misleading.

Hormone Excretion Pattern (Table II)

Follicle-stimulating hormone was increased above normal in all cases examined. The scatter appears to be wider, and levels on the whole lower, in the chromatin-negative group, but the difference between the two does not reach significance (Table III). In each group there appears to be a rough parallelism between the level of follicle-stimulating hormone and size of testis.

17-ketosteroid excretion. In one chromatin-negative case the total daily urinary excretion of 17-ketosteroids is decreased. In all cases α and β fractionation shows normal proportions. In spite of normal total 17-ketosteroid excretion most chromatin-positive and some chromatin-negative cases have clinical features generally attributed to lack of androgens.

Oestrogens. Oestrone is decreased in one chromatin-positive and two chromatin-negative cases, oestradiol is increased in one chromatin-positive case, and oestriol is decreased in two chromatin-positive cases. There does not appear to be any kind of correlation with any clinical features.

TABLE III

Comparison of Means of Measured Quantities

	Mean values			*Significant differences between pairs of mean values*		
	K+	*K−*	*N*	*K+/N*	*K+/K−*	*K−/N*
Height (inches)	69·0	66·4	66·6	Sig.	Sig.	—
Span (inches)	70·6	68·8	69·0	—	—	—
Crown to pubis (inches)	33·2	32·8	32·8	—	—	—
Sole to pubis (inches)	35·8	33·6	33·8	Sig.	Sig.	—
Span minus height (inches)	1·6	2·4	2·5	Sig.	Sig.	—
Sole to pubis minus crown to pubis (inches)	2·6	0·8	1·1	Sig.	Sig.	—
Left testis: length (cm.)	1·8	2·9	5·1	Sig.	Sig.	Sig.
Right testis: length (cm.)	1·8	3·0	5·1	Sig.	Sig.	Sig.
Follicle-stimulating hormone (mouse units/day)	67·3	53·5	5·0	Sig.	—	Sig.
Shaves per week	3·8	4·9	5·5	Sig.	—	—
Age shaving commenced	18·9	17·3	17·6	—	—	—

K+ = chromatin-positive, *K−* = chromatin-negative Klinefelter's syndrome, *N* = controls.
Sig. = significant difference between pairs of means ($P < 0{\cdot}05$ by t test).

TABLE IV

Comparison of Features Graded Arbitrarily

	Significant differences between pairs		
	K+/N	*K+/K−*	*K−/N*
Prostate size	Sig.	Sig.	—
Abdominal hair	Sig.	—	Sig.
Facial hair	Sig.	—	—
Gynaecomastia	Sig.	—	—

Abbreviations as Table III.

Other Features

Chromatin-positive patients shave less frequently than normal (Table III), and there are significant differences (Table IV) in the distribution of facial and abdominal hair and in respect of prostate size. Gynaecomastia is more common, and biopsy in two cases demonstrated epithelial hyperplasia of the ducts and periductal fibrosis. These patients start shaving on the average at a later date (Table III) than normal. Late puberty, judged in this way, seems to correlate with the presence of eunuchoid measurements, but the trend is not significant; Case 7 is an obvious exception. The chromatin-negative patients have significantly less abdominal hair than normal (Table IV). Our data are insufficient to determine whether or not a tendency of chromatin-

negative cases (Table III) to occupy an intermediate position between chromatin-positive and normal in respect of face hair, gynaecomastia, and frequency of shaving, is real.

Aetiological factors. Possible causes of testicular atrophy were uncovered in the history of most patients, but it seems very unlikely that these were of any significance. The commonest was mumps, but in every case this was a childhood illness which did not include orchitis. In any event it is clear from inspection of Table II that these various factors are just as common in the chromatin-positive patients and in the controls as in the chromatin-negative patients, in whom alone any question of exogenous damage to the testes arises. Three chromatin-negative patients who had bilateral herniorrhaphies in childhood present the only difficulty in this respect; and even here the presence of single similar cases in each of the other groups, and the absence of any detectable difference between these three cases and the rest of the chromatin-negative group, leads us to believe that the herniae, though very possibly an associated anomaly, are not in themselves the direct cause of the testicular lesion.

Subdivision of the chromatin-negative group. The two histological variants (the accepted groups with fibrosis and hyalinization of tubules, and the 'del Castillo' group with absence of germ cells, distinguished as F and A in Table II*a*) show no obvious difference in any of the features studied. The tendency to smaller size of testis in the F group may simply reflect the histological difference. We have not been able to establish any other criteria on which it appeared to be profitable to base a subdivision of the group, but clearly examination of larger series of cases is necessary.

Discussion

The main purpose of the present paper is to stress clinical features in diagnosis, and to report the significant differences noted. In particular we wish to draw attention to the value of the sole-to-pubis measurement in diagnosis, and to point out that the span-height difference is misleading. The increased height of chromatin-positive patients has been noted by Raboch (1957). Although our measurements are not strictly comparable, we cannot accept his conclusion that the trunk measurement is reduced in these cases, and indeed we do not see how his own data support this. The leg lengthening, without corresponding lengthening of the arms, is of interest, and appears to be characteristic of this form of eunuchoidism.

The female genetic sex of chromatin-positive cases seems to manifest itself in their significantly small testes, small prostates, reduced facial and abdominal hair, and enlarged breasts. Though these might be thought to be the result of some endocrine defect, our hormone excretion studies, so far as they go, show no real evidence of androgen shortage or of excess of oestrogen. In many cases a diagnosis of chromatin-positive Klinefelter's syndrome can be made with reasonable certainty on purely clinical grounds, but for confirmation nuclear sexing is required. In chromatin-negative cases, although size of

testis and distribution of abdominal hair may provide a clue, clinical diagnosis is less certain. Even estimations of follicle-stimulating hormone may be equivocal, and confirmatory testicular biopsy is always advisable. In Klinefelter's syndrome in general the most useful single clinical diagnostic feature is testicular size, but, while in chromatin-positive cases the testes are always much smaller than normal, the chromatin-negative cases occupy an intermediate position and may cause difficulty at each end of their range. Though, of course, other causes of testicular atrophy must be eliminated, the presence of small testes is so much the most constant clinical feature of such cases that we have elsewhere suggested (Ferguson-Smith, Lennox, Mack, and Stewart, 1959) that 'primary micro-orchidism' might well be adopted as a name for this somewhat unsatisfactorily labelled disease. (Our views are not unanimous: Stewart (1958) has suggested, as part of an attempt to bring the nomenclature of this and some related conditions into line with their developmental origin, the name 'medullary dysgenesis'.)

The status of chromatin-negative Klinefelter's syndrome has perhaps been established a little more firmly by these investigations. At least we have been able to show that it constitutes a reasonably homogeneous group, only a little less well defined than the more striking chromatin-positive sex-reversed cases, to which, in spite of some clear-cut points of distinction, they bear in many respects the closest analogy. Elsewhere we have presented evidence from family studies suggesting that aetiologically the two conditions may derive from comparable though distinct genetic mechanisms (Stewart, Ferguson-Smith, Lennox, and Mack, 1958).

Incidence. It is hard to be certain of the relative incidence of the two forms. Nearly all such estimates are vitiated by the fact that the chromatin-positive form can be diagnosed with relative ease and confidence by means of the oral mucosal smear, so that surveys of large numbers of patients are readily done (Ferguson-Smith, 1959; Moore, 1959), while no equally simple method is available for the collection of chromatin-negative cases. It is because of this, we believe, that most authors accept estimates like that of Nelson (1956), who found the chromatin-positive form to be five times as common as the chromatin-negative. Our own patients attending an infertility clinic, among whom (because testicular biopsy can justifiably be performed whenever it seems likely to add any information about the patient concerned) it has been possible to ascertain the incidence of chromatin-negative cases with the same exactitude as the chromatin-positive, seems to give a more accurate assessment, and suggests (Ferguson-Smith, Lennox, Mack, and Stewart, 1957) that the chromatin-negative form is in fact rather the more common of the two. The true incidence of the chromatin-positive form is now known with some approach to accuracy. In Glasgow it cannot be less than 1 in 3,000 (Ferguson Smith, 1959), and we believe it to be about 1 in 1,000 apparent male subjects. Prader, Schneider, Frances, and Zublin (1958) give a figure of approximately 1 in 1,000 for Zürich. Moore (1959) found five genetic females (presumably all examples of Klinefelter's syndrome) in 1,900 apparent male infants born in Winnipeg—

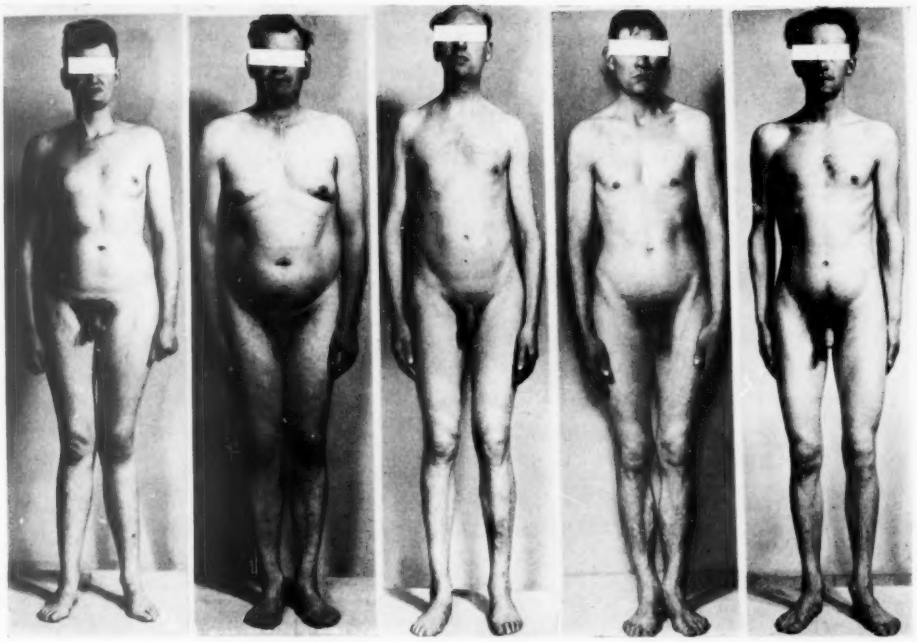
an incidence of 1 in 380. We are probably safe in assuming that about 0·1 to 0·2 per cent. of all phenotypic males are examples of chromatin-positive Klinefelter's syndrome, and that a slightly higher percentage fall into the chromatin-negative group. Comparison of these figures with the estimates available of the approximate incidence of male infertility in this country (Campbell, 1958) confirm the estimate, made on figures from our own infertility-clinic, that Klinefelter's syndrome may account for something like one-third of all cases of high-grade organic infertility in the male.

Management. Although not our primary concern, a final note on the clinical management of these patients is apposite. The most important single thing in their management is that they should not know the result of nuclear sexing. Indeed, they should have no hint as to the nature of the investigation. The chromatin-positive patients should not know that they are other than completely male, and the chromatin-negative patients should not know that their sex was ever sufficiently in doubt for nuclear sexing to be carried out. Barr (1956) has stressed the fact that the terms chromatin-positive and chromatin-negative are valuable in avoiding psychological stress to the patient. There is no question of changing the phenotypical sex from that of male, and hormone therapy, where necessary, should be directed to developing male secondary sex characters. In spite of normal 17-ketosteroid levels, some of these patients appear clinically to lack androgens, and testosterone has been used with good effect in some who complained of muscular weakness or loss of libido. Some of our patients have been aware of their subnormal masculinity and, although the question of sex change was never put to them directly or indirectly, a few have confessed to fears in this respect. They have readily accepted our reassurance that they are normal males, but that a mild glandular upset is present, and that treatment for this condition can be given if they wish or require it in later years. As with all subfertile patients, we have allowed realization of their inability to procreate to dawn slowly, in order to minimize psychological stress. Such treatment is particularly necessary in the chromatin-positive group of patients, who already lack confidence in themselves, and who are frequently emotionally immature. They have been advised that infertility is common, and have accepted the view that they are unfortunate but not abnormal. The main thing that we have been able to do for them is to allay their fears and, where necessary, to give testosterone.

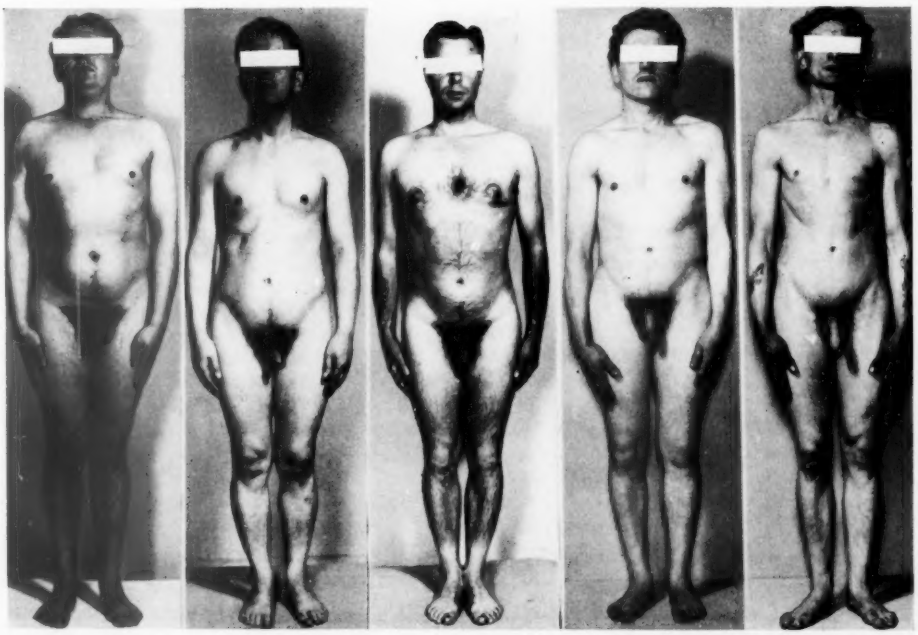
Summary

1. A systematic comparison of a number of clinical features and the results of hormonal estimation has been made in groups of patients exhibiting chromatin-positive Klinefelter's syndrome (16 cases) and chromatin-negative Klinefelter's syndrome (16 cases), and in a group of 16 fertile males, all derived from a single infertility clinic.

2. Significant differences from normal were found in respect of both forms of the disease in testicular size, prostate size, excretion of follicle-stimulating



Case 25 Case 1 Case 4 (shaved) Case 30 Case 3



Case 12 Case 17 Case 14 Case 20 Case 21

Five chromatin-positive cases (*above*) and five chromatin-negative (*below*): representative samples arranged in order roughly of decreasing eunuchoidism. Eunuchoidism is rather more marked in the chromatin-positive group, gynaecomastia more frequent, and the legs longer; but in both groups a fully masculine habitus predominates

hormone, and distribution of abdominal hair; in the chromatin-positive form additional differences from normal were found in sole-to-pubis length, facial hair, frequency of shaving, and incidence of gynaecomastia.

3. While excretion of follicle-stimulating hormone was increased in every case, no abnormalities were found in the patterns of ketosteroid or oestrogen excretion.

4. Chromatin-positive eunuchoid subjects have long legs, but little or no lengthening of the arms, so that the ordinary measurement of span-height difference is misleading.

5. Cases of chromatin-negative Klinefelter's syndrome probably form a reasonably well-defined group of uncertain but possibly genetic aetiology; cases of the 'del Castillo' type, with germ-cell deficiency, behave in the same way as those with the accepted testicular histology.

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FAMILIAL DIABETES INSIPIDUS[1]

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The occurrence of excessive thirst and polyuria as a familial trait is unusual, but has been described for over a century. Lacombe (1841) is credited with the first account (Blotner, 1951), but the best known family study, which eventually included 35 cases, is that of the Weils (Weil, 1884; Weil, 1908; Camerer, 1935). The literature has been reviewed by Forssman (1945) and Blotner (1951). It is only in recent years that the condition of true familial diabetes insipidus, with failure or partial failure of production of antidiuretic hormone, as an isolated defect, has been distinguished from a congenital renal tubular defect of water reabsorption (Williams and Henry, 1947; Forssman, 1954). In the former condition the patients are normally sensitive to pitressin, but the latter is pitressin-resistant or 'nephrogenic' diabetes insipidus. The purpose of the present paper is to record the pedigrees of two examples of hereditary diabetes insipidus, and to describe investigations carried out to determine the site of the defect in the production of antidiuretic hormone.

Family A

This family, the pedigree of which is shown in Fig. 1, was investigated after the chance remark of one member (IV. 13) that many members of his family were 'drinkers'. In all, 82 members of the family were traced, through six generations, back to the immigration from Cornwall to Australia of the great-grandfather about 100 years ago. Thirty-one patients were personally interviewed; 15 others answered postal questionnaires; the remainder were assessed by descriptions obtained from their close relatives. Members of past generations were classified according to the independent account of their drinking habits by at least two of their descendants. In nine instances the presence or absence of diabetes insipidus was established by the response of a water diuresis to the infusion of hypertonic saline. In 22 others the clinical diagnosis was confirmed by estimation of the specific gravity of urine after fluid deprivation for at least eight hours. In this family the urine of those affected was found always to have a specific gravity below 1,006 (except in one male member (V. 26) who had an unrecognized glycosuria), and in the absence of albuminuria a fasting specific gravity greater than 1,012 was taken to indicate normal pituitary function. It was striking that both affected and non-affected members accepted excessive

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drinking as a family habit, and as a result minimized their own and their relatives' polydipsia and polyuria, thus tending to underestimate the number of people suffering from diabetes insipidus. From the information obtained the pedigree shown in Fig. 1 has been constructed.

Family B

This smaller and apparently unrelated group was investigated on the same plan as Family A, and the pedigree is shown in Fig. 1. The propositus (II. 5) was given a hypertonic saline infusion; in eight other members the diagnosis was confirmed by urinary specific gravity. The earliest traced member of this family was of Swedish extraction.

Physiological Investigations

In nearly all cases the clinical evidence as to the presence or absence of diabetes insipidus was unequivocal. Since, however, the nature of the defect in the production of antidiuretic hormone in this condition had not previously been investigated, an attempt was made to elucidate the problem by assessing the effect of both hypertonic saline and intravenous nicotine. The hypertonic saline test was a modification of the method of Carter and Robbins (1947). A water load of 20 ml. per kg. was given orally over a period of 30 minutes, and one hour later, provided the urine flow was greater than 5 ml. per minute, an intravenous infusion of 3 per cent. saline (0·25 ml. per kg. per minute) was commenced, and continued for 45 minutes. The patients voided urine every 30 minutes, and were not catheterized. If there was no significant reduction in urine flow 30 minutes after the end of the saline infusion, five units of aqueous pitressin (Parke Davis) were injected intramuscularly, and the collection of urine continued for a further 60 minutes. The normal response is shown in Fig. 2, which represents the mean response of six normal subjects investigated by this method. Fig. 3 shows the response of a clinically unaffected male subject (V. 13), which does not differ from the normal.

It was noticed that there was considerable individual variation in the clinical severity of the condition in affected members. For example, of two brothers in Family A (IV. 10 and IV. 12), the former had had a gross thirst all his life, with a fluid intake of seven to eight litres per day, and became very uncomfortable if deprived of fluid for longer than four hours; his younger brother, although admitting to occasional nocturnal drinking, was much less affected, and could sleep through the night without fluid if required. It appeared that this clinically milder case might be an example of partial failure of production of antidiuretic hormone. Both these patients were subjected to a hypertonic saline test (Figs. 4 and 5). In the clinically more severe case (IV. 10) there was a slight antidiuresis in response to hypertonic saline, while there was no response in the apparently milder case (IV. 12). Nine members of Family A were subjected to infusion with hypertonic saline (IV. 10, 11, 12, 13, 14; V. 9, 13, 18, 33), and one

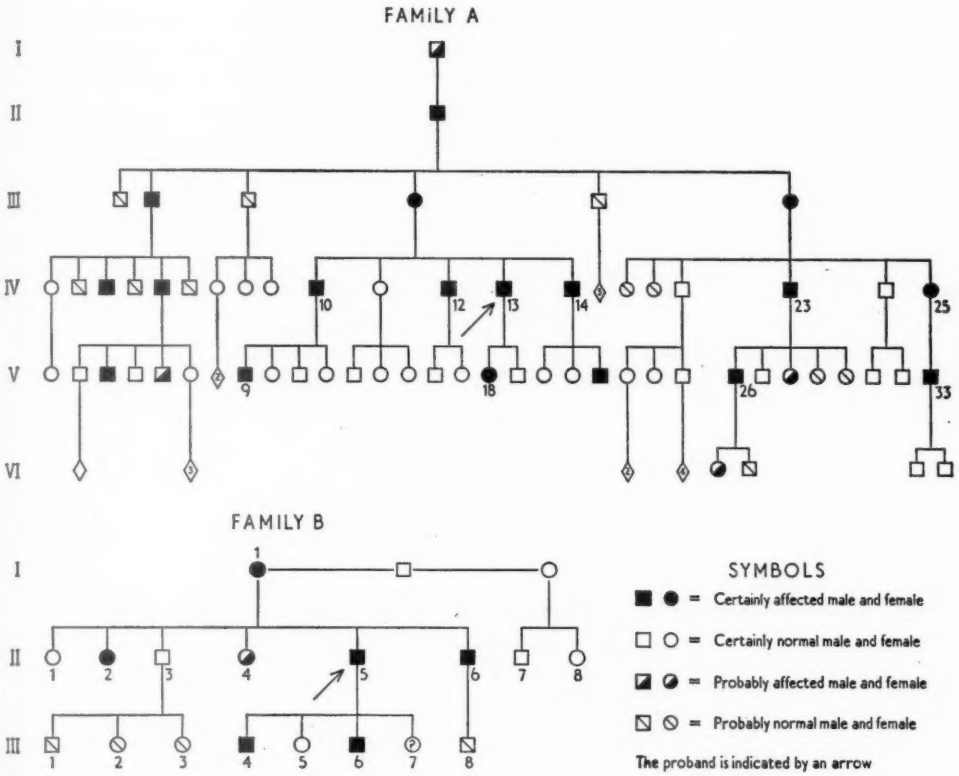


FIG. 1. Pedigrees of Family A and Family B.

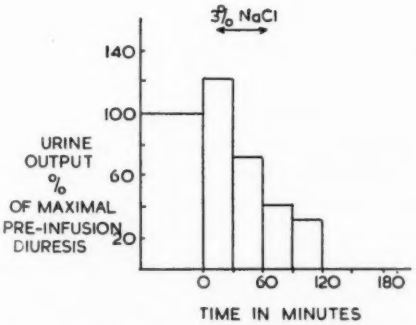


FIG. 2. The mean response of six normal subjects to hypertonic saline.

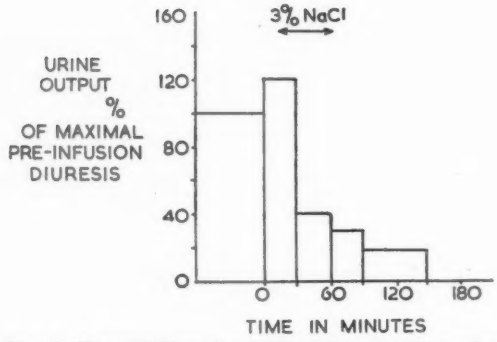
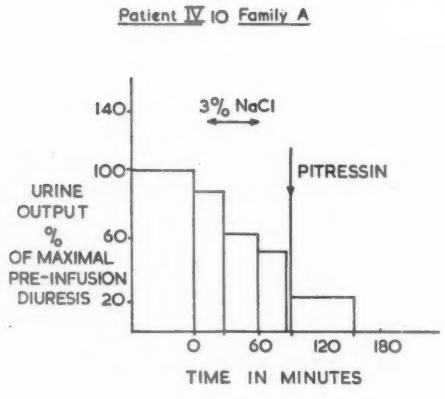
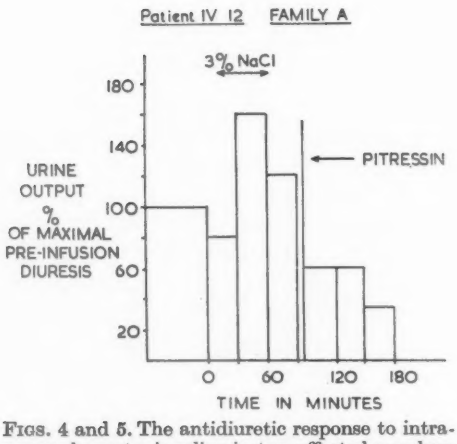


FIG. 3. The antidiuretic response of a normal member of Family A (V. 13) to intravenous hypertonic saline.





FIGS. 4 and 5. The antidiuretic response to intravenous hypertonic saline in two affected members of Family A (IV. 10 and IV. 12).

member of Family B (II. 5). The responses in patients with diabetes insipidus were all similar to those shown in Figs. 4, 5, and 6.

It is known that nicotine, either by injection or by inhalation, as in cigarette smoke, produces an antidiuresis in normal persons (Burn, Truelove, and Burn, 1945). Three of the affected members of Family A were tested by this method.

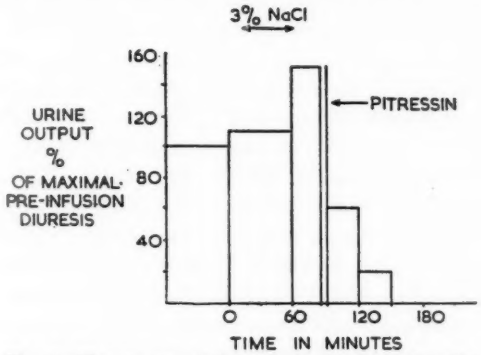


FIG. 6. The response to intravenous hypertonic saline in one affected man (II. 5) in Family B.

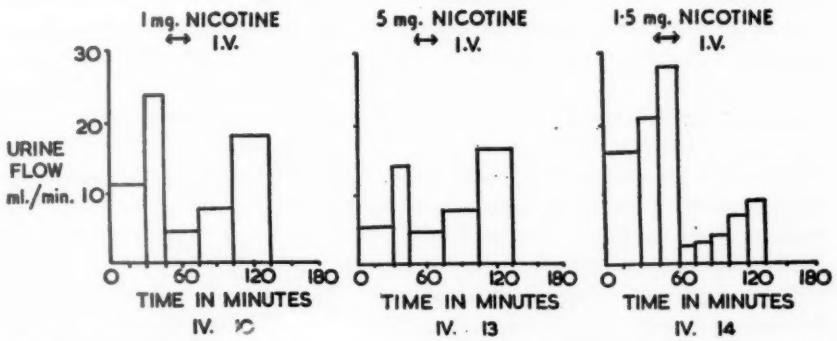


FIG. 7. The antidiuretic effect of intravenous nicotine acid tartrate in three patients with familial diabetes insipidus in Family A.

A solution of nicotine acid tartrate (1 mg., containing approximately 30 per cent. nicotine, per ml.) was injected slowly into a vein after induction of a water diuresis; the method previously used by Cates and Garrod (1951) and Chalmers and Lewis (1951) was closely followed. The patients were not catheterized, but passed urine at 15-minute intervals before the injection of nicotine, and at 30-minute intervals subsequently. The responses of three members of Family A (IV. 10, 13, and 14) are shown in Fig. 7. The doses varied: IV. 10, a non-smoker, received 1 mg. of nicotine, but IV. 13, a heavy smoker, received 5 mg. Toxic effects were mild; vertigo and nausea, and in one case transient local irritation, were the only effects noted. In each case a short-lived but definite antidiuresis followed the injection of nicotine, and the response in all cases was similar in spite of the different doses used.

Discussion

Clinical features. In common with other reported families (Ellerman, 1939; Pender and Fraser, 1953), the families here reported showed great individual variation in the degree of their symptoms. Even where two members were closely related, with apparently the same degree of defect (Figs. 4 and 5), the fluid exchange in one could be between seven and eight litres and in the other between three and four litres per day. The explanation is not clear, but may lie in differences in end-organs, such as the sensitivity of the renal tubules, or in the fact that in some cases there is not complete absence of antidiuretic hormone. The age at onset of the condition also appears to be variable. In Family B the condition was detected in both the children (III. 4 and III. 6) at six months by their thirst and polyuria, and by their crying at night, which was appeased only by water. The other members of this family also appear to have had the condition since infancy. In Family A, however, although in most cases the condition was noticed in early life, two members of the fifth generation, which was the best documented group in the series, were not noticed to be drinkers until the age of seven or eight. In this respect it is important to remember that the parents and relatives in both families usually take a keen interest in the fluid balance of any young children, and so should be more likely to notice excessive drinking in infancy than if they were not forewarned. A similarly late age of onset has been recorded before (Chester and Spiegel, 1933; Forssman, 1945), but is apparently unusual. Blotner (1951) believed that the reason why most cases are recognized in the second year of life is that the infantile kidney does not concentrate urine well, so that some degree of polyuria is usual in babies. The affected members commonly noticed that by the sixth decade the craving for water had decreased, even though there was no change in the specific gravity of the urine. In nearly all cases the condition is thought to be at its peak in adolescence or young adult life.

The symptoms are usually characteristic. Besides the history of excessive intake and output, which is often discounted, there is nearly always nocturnal drinking, and in all cases a preference for water. All the affected members whom I have interviewed have insisted that only water will satisfy their thirst, and that it is preferred iced if possible. This peculiarity has been stressed by Thomas (1957) as a general feature of diabetes insipidus. The other striking feature in both families is the manner in which they regard the condition as a family habit. Thus, until one member at the age of 45 became tired of broken sleep, none of the siblings (IV. 10 to 14) had ever sought advice for this condition. Further, one of them, while in hospital after a haematemesis, had convinced the nursing staff and the resident medical staff that a daily fluid exchange of eight to nine litres was normal for him. In general, although a few patients had had pitressin injections as children, most preferred to do without it.

Genetic aspects. The inheritance of polyuria and excessive thirst in most of the larger families is consistent with the presence of a simple dominant gene (Weil, 1908; Gansslen and Fritz, 1924; Chase, 1927; Ellerman, 1939; Pender and

Fraser, 1953; Levinger and Escamilla, 1955). Both the families described here appear to be examples of diabetes insipidus inherited as a simple dominant characteristic; that is, the inheritance has always been direct, and every affected member has an affected parent. In addition, sex-linkage is excluded, as in each pedigree there occur both father-to-son transmission and the presence of a normal daughter of an affected father. It was noticed that the proportion of affected male to affected female subjects in the whole pedigrees was 16 to six in Family A and four to three in Family B. This male predominance has been a frequent feature in previously reported families, in some of which the condition had skipped generations (Gee, 1877; McIlraith, 1892), suggesting the presence of a recessive gene or incomplete penetrance. Forssman (1945) reviewed this question both from his own cases and from previous records. He suggested that the inheritance of pitressin-sensitive diabetes insipidus was due to a sex-linked recessive gene in some families, and subsequently he has been able to demonstrate this fact convincingly (Forssman, 1954). He emphasized the fact that the female heterozygote carriers were, at most, only slightly affected. The same author also analysed the reported series in which the inheritance was unquestionably dominant, and found that the proportion of affected male to affected female members was three to two (Forssman, 1945). He believed that this excess of male sufferers was due to an unequal selection of cases favouring men, because father-to-son inheritance was an essential criterion for dominant inheritance. Since there was a male predominance in the present series, a further review of the reported families has been undertaken. Seven series in which the inheritance of diabetes insipidus was due to a dominant gene were analysed. Only those generations in which information on all siblings was available were included. The offspring of affected parents were divided into male and female, affected and non-affected, except that the probands (five male and two female members) were excluded when their immediate generation was considered. In these series the initial criterion of dominance was direct inheritance, and in three of them father-to-son transmission was not discussed. They have been chosen for analysis because they represent the largest well-documented families with simple dominant inheritance of which reports are available. The results are shown in the Table. It is apparent that there is a deficiency of affected female members as compared with the expected figure; further, when this difference is considered statistically, with the premiss that the expected incidence of affected and non-affected female members is equal, the χ^2 test gives the result $P = 0{\cdot}07$. There is no such difference between the number of affected and non-affected male members, nor is there any difference in the sex incidence of the offspring of affected men and women. That this indicates a real deficit of affected female subjects is suggested by considering whether female members predominate over male members in each series. Among non-affected subjects, female members predominate in four of the seven families analysed, whereas among affected subjects they predominate in only one family. Further analysis was performed to test Forssman's hypothesis that selection is unequal, favouring male patients. The ratio of

affected male to affected female members was considered in six pedigrees, after two affected male members had been excluded from each. The pedigree of Levinger and Escamilla was excluded from this analysis, because in the generations considered in the Table there was no instance of father-to-son transmission. This procedure gave a ratio of 67 affected male to 56 affected female members. It is of interest that the two apparently unrelated families reported from North America (Pender and Fraser (1953) and Levinger and Escamilla (1955)) do not show this female deficit. The reason for this deficit of

TABLE

The Number of Affected and Non-affected Male and Female Members in Familial Diabetes Insipidus with Dominant Inheritance

	Male		*Female*		
Author	*Affected*	*Non-affected*	*Affected*	*Non-affected*	*Proband*
Ellerman (1939) . . .	12	13	9	11	Male
Gansslen and Fritz (1924) .	7	3	9	11	Male
Levinger and Escamilla (1955)	5	5	10	8	Female
Martin A (1959) . . .	13	16	5	12	Male
Martin B (1959) . . .	3	1	2	2	Male
Pender and Fraser (1953) .	21	29	15	18	Female
Weil (1908) . . .	18	14	14	25	Male
Total	79	81	64	87	

female sufferers, in the presence of an apparently simple dominant type of heredity, is obscure. There is no obvious genetic mechanism which will explain such a circumstance at present. It is possible, however, that the condition may be lethal to female infants *in utero* or in early life. There was no suggestion that this was the case in the present series, but unfortunately no detailed information as to the incidence of abortions or still-births was obtained, nor is such information available in published reports. It is planned to investigate Family A in the present series further, using other genetic indices, and it is hoped that other reported families will be similarly studied.

Pathogenesis. There has been no serious attempt to discover the site and nature of the lesion which results in failure of production of antidiuretic hormone in this familial condition. Autopsy reports have been very rare, and Forssman (1945), in his extensive review, could find only two. The lesions described have been a reduction in cells in the region of the supra-optic nucleus, and of nerve fibres in the posterior pituitary stalk. The whole subject of the pathogenesis of diabetes insipidus has recently been reviewed by Sloper (1958). Verney (1946) showed that the osmoreceptors which controlled the secretion of the antidiuretic hormone were situated somewhere on the branches of the carotid arteries. The hypertonic saline test presumably produces antidiuretic hormone by stimulation of these receptor cells. In the patients described the hypertonic saline test gave a clear differentiation between those who were affected and those who were not. This test, however, gives no information as to the site of the defect, that is, whether there is a central failure of production of antidiuretic hormone, or whether the osmoreceptors fail to respond to the osmotic stimulus.

The release of antidiuretic hormone can be produced by other stimuli besides variation in the osmotic pressure of blood; in particular, emotion (Verney, 1946) and acetylcholine (Pickford, 1939) have been shown to be effective in animals. Burn, Truelove, and Burn (1945) showed that the action of acetylcholine could be reproduced exactly with nicotine in animals, and then obtained similar responses in human volunteers. Walker (1949) and Chalmers and Lewis (1951) confirmed these observations in normal human subjects, using both cigarette smoke and intravenous nicotine acid tartrate. Subsequently it has been reported that smoking causes an increase in the antidiuretic activity of urine (Taylor and Walker, 1951) and of blood (Lee and Bisset, 1958). The use of nicotine for the diagnosis of diabetes insipidus was described by Lewis and Chalmers (1951) and Cates and Garrod (1951). The antidiuretic action of acetylcholine and nicotine was shown by Pickford (1939) and Burn, Truelove, and Burn (1945) to depend on the presence of an intact posterior pituitary gland, and subsequently Pickford (1947) showed in animals that the site of action was primarily in the hypothalamus. All accounts of the clinical use of nicotine have emphasized the fact that tolerance to the drug is common, and that non-smokers in general require smaller doses than heavy smokers to produce both antidiuretic and toxic effects. Thus the three people in Family A to whom nicotine was given included one smoker and two non-smokers. The dose used varied from 1 mg. to 5 mg. of nicotine base, according to the production of mild toxic effects such as vertigo and nausea. The antidiuretic response produced was similar in each case, suggesting that the action of the drug was the same. An antidiuretic response to nicotine in patients with diabetes insipidus in whom there is no response to hypertonic saline was previously described by Lewis and Chalmers (1951), who suggested that this phenomenon was due to an isolated failure of osmoreceptors. This belief was supported by the detailed studies of Dingman, Benirschke, and Thorn (1957), who described three cases. The latter authors were able to produce pathological evidence, in one patient with metastatic carcinoma, that the hypothalamus was intact, but that the posterior portion of the pituitary gland was completely destroyed. Cates and Garrod (1951) also noted a response to nicotine in clinical diabetes insipidus, but suggested that such cases were examples of partial lesions, in which nicotine was a stronger stimulus than hypertonic saline. This suggestion is in accord with the occurrence of temporary diabetes insipidus with complete recovery, and with the varying degrees of clinical severity of the condition. There is thus evidence that diabetes insipidus can be produced by lesions at various sites, in particular the hypothalamus, the posterior pituitary, and the osmoreceptors. The present study does not prove the site of the lesion in familial diabetes insipidus, but suggests that it may be due to a failure of the osmoreceptor mechanism rather than a defect in hypothalamic production of antidiuretic hormone.

The author wishes to thank Professor A. G. Steinberg, of Western Reserve University, Cleveland, for his interest and advice in the genetic discussion.

He is also grateful to Dr. John Game and Dr. Bryan Hudson, of the Alfred Hospital, for directing his attention to this problem. The work was carried out during the tenure of the George Merriman Research Scholarship of the Alfred Hospital, Melbourne.

Summary

Two unrelated families are described which showed congenital pitressin-sensitive diabetes insipidus due to a dominant gene.

A greater incidence of affected male as compared to affected female patients was found both in the present series and in a review of previously reported pedigrees. The incidence of affected male and female subjects has been analysed, but the explanation of the deficiency of affected female subjects, occurring in the presence of an apparently simple dominant gene with complete penetrance, is not clear.

The clinical features of the condition are described, and the results of attempts to stimulate the production of antidiuretic hormone by intravenous hypertonic saline and nicotine are reported. There is evidence that the defect in familial diabetes insipidus may be primarily in the osmoreceptor mechanism rather than at the site of production of antidiuretic hormone.

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THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1959

FIFTY-THIRD ANNUAL GENERAL MEETING

THE FIFTY-THIRD ANNUAL GENERAL MEETING was held at the Reardon Smith Lecture Theatre, Cardiff, on Friday and Saturday, April 10 and 11. The attendance book was signed by 217 members and 54 visitors.

The President, Dr. J. R. H. Towers, was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read, confirmed, and signed. The following Officers, Executive Committee, and Honorary, Senior, and Ordinary Members were elected unanimously, as was the new member of the Editorial Board:

Executive Committee

President: Professor Harold Scarborough.

President-Elect: Dr. Donald Hunter.

Treasurer: Dr. C. M. Fletcher.

Secretary: Dr. R. I. S. Bayliss.

Members for England and Wales:
Professor D. V. Hubble.
Dr. K. Robson.
Dr. C. N. Armstrong.
Professor A. Kekwick.
Professor Melville Arnott.
Dr. R. Bodley Scott.

Members for Scotland:
Professor D. M. Dunlop.
Dr. J. H. Wright.
Professor R. B. Hunter.

Members for Ireland:
Dr. J. T. Lewis.
Dr. M. G. Nelson.
Dr. S. Dundon.

Election of Honorary Member

Sir Rudolph Peters.

Election of Senior Members

Dr. A. C. Hampson.
Dr. M. Shaw.

Election as Member of the Editorial Board

Professor R. B. Hunter.

Election of Ordinary Members

Harold Wykeham Balme, M.D., M.R.C.P., Physician, St. Bartholomew's Hospital.
Hugh Brebner, M.D., M.R.C.P., Physician, Western Infirmary, Glasgow.
William John Hughes Butterfield, M.D., M.R.C.P., Professor of Experimental Medicine, Guy's Hospital.

Theodore Moir Chalmers, M.D., M.R.C.P., First Assistant, The Medical Unit, Middlesex Hospital.

Timothy Brendan Counihan, M.D., M.R.C.P., Professor of Medicine, University College, Dublin.

Grant de Jersey Lee, M.D., M.R.C.P., First Assistant to the Regius Professor of Medicine, University of Oxford.

Thomas Roger Edward Pilkington, M.D., M.R.C.P., Senior Lecturer in Medicine, St. George's Hospital.

Thomas Arthur John Prankerd, M.D., M.R.C.P., First Assistant, Medical Unit, University College Hospital.

Michael James Riddell, M.D., M.R.C.P., Physician, Victoria Infirmary, Glasgow.

James Sharp, M.D., M.R.C.P., Senior Lecturer in Rheumatology, Royal Infirmary, Manchester.

John Parsons Shillingford, M.D., M.R.C.P., Physician, Hammersmith Hospital.

John Bernard Stanton, M.B., M.R.C.P., Neurologist, Northern General Hospital, Edinburgh.

Gerald Trevor Thomas, M.B., M.R.C.P., Physician, Canadian Red Cross Memorial Hospital, Taplow.

David Verel, M.D., M.R.C.P., Senior Lecturer in Medicine, Sheffield University.

Richard Arthur Womersley, M.D., M.R.C.P., Lecturer in Medicine, Queen's University, Belfast.

Election of Overseas Ordinary Members

Alexander Gordon Bearn, M.D., Associate Professor, Rockefeller Institute, New York.

Alexander Brown, F.R.C.P., Professor of Medicine, University College of West Africa, Ibadan.

Eric Kennedy Cruickshank, M.D., F.R.C.P., Professor of Medicine, University College of the West Indies, Jamaica.

Alexander James Smith McFadzean, F.R.C.P., Professor of Medicine, University of Hong Kong.

Hugh Norwood Robson, F.R.C.P. (Ed.), Department of Medicine, University of Adelaide, Australia.

The Treasurer, in presenting his accounts, said that during the year the bank balance had declined by nearly £100, but since the capital reserve was nearly £4,000 he did not regard this as a serious matter at present. He hoped to improve the interest on investments by reinvesting in equity stocks.

Place of Meetings 1960 and 1961. Dr. Donald Hunter invited the Association to meet at the London Hospital in 1960, and this was accepted with pleasure and anticipation. Professor Bruce Perry's invitation to meet in Bristol in 1961 was reaffirmed and again accepted.

The President paid tribute to Professor Dunlop who had served for so long and so conscientiously on the Editorial Board and was now retiring from this post.

The newly elected President, Professor Harold Scarborough, then took the Chair.

SCIENTIFIC BUSINESS

Friday Morning, April 10

1. Dr. William Phillips explained that the *Welsh National School of Medicine* was young because as a city Cardiff was young. Until 200 years ago Wales was pastoral and agricultural, and the first train of coal did not leave the Rhondda Valley until 1855. Thereafter Cardiff expanded rapidly and a town, which 100 years ago comprised two parishes and had eight doctors, became before the First World War the greatest coal-exporting city in the world.

University education in Wales began in Aberystwyth in 1872, and it was not until 1883 that a University College was opened in Cardiff. In 1894 an embryo Medical School, comprising departments of anatomy and physiology with part-time teaching in materia medica, was formed as part of the College, which devoted what seemed to many a disproportionate part of its slender financial resources to this new venture. The problems of further development were answered by a Royal Commission on University Education in Wales, which recommended in 1918 that a National Medical School should be established

as a separate College within the federal University of Wales, the other members being the University Colleges of Aberystwyth, Bangor, Cardiff, and Swansea. A remarkable recommendation, made to the Commission by the medical staff of the day, was to adopt the Unit system, which was at that time untried in Great Britain, although it had been discussed at length by the Royal Commission on the University of London. The clinical school, in the main based on the Unit system, commenced in 1921, but did not become an independent part of the University until 1931. Even now the pre-clinical departments, to the great regret of the Medical School staff, remained within the University College and were physically separate.

The Unit system had been for so long an integral part of the Medical School that it was important to record an opinion generally, and probably unanimously, held by the present teachers that no other arrangement seemed so satisfactory, unless a complete University Hospital were conceived.

2. DR. A. H. JAMES said that *Alcohol-induced Pain in Hodgkin's Disease* occurred in one-sixth of patients. He had compared 13 patients who had this symptom with 20 who did not. Three observers had assessed the prominence of certain histological features in lymph-nodes from each case, not knowing from which group the glands came. Sections from patients with alcohol-induced pain showed fewer reticulum-cell mitoses, and more eosinophils and fibrosis. The prominence of reticulum cells, neutrophils, plasma cells, and necrosis, did not differ significantly in the two groups. Fibrosis was often macroscopically obvious in glands from patients with alcohol-induced pain. The histological picture did not differ according to whether or not the pain had been felt in the particular group of nodes taken for biopsy. Turning to the clinical features, DR. JAMES said that patients, who at the time of biopsy or later had alcohol-induced pain, more often had spontaneous pain than the control group; mediastinal nodes were more frequently enlarged, and a leucocytosis more common. The groups did not differ in the incidence of malaise, itching, tenderness of nodes, enlargement of the liver or spleen, fever, or anaemia. Because changes had been demonstrated in nodes not the site of alcohol-induced pain in patients who felt it elsewhere, DR. JAMES rejected any immediate causal relationship between the pain and the unusual histology. He thought it probable that the two groups represented distinct entities. This idea was confirmed by a lack, in patients with alcohol-induced pain, of the preponderance of male subjects usually found in Hodgkin's disease.

In reply to DR. J. G. SCADDING, DR. JAMES said that the retrospective nature of the survey precluded a comparison of prognosis in the two groups, but there was no apparent difference. In reply to DR. HOWAT, he said that he had not studied the effect of histamine or serotonin, but Bichel and Bastrup-Madsen (*Lancet*, 1953, **1**, 764) had reported that administration of histamine did not reproduce the pain. Nor could he tell PROFESSOR BYWATERS whether alcohols other than ethyl alcohol induced the pain.

3. DR. C. B. MCKERROW (introduced by DR. J. C. GILSON) described further *Physiological and Pharmacological Experiments into the Cause of Byssinosis*, as a sequel to the work presented at the Edinburgh meeting of the Association in 1957, when it was shown that there was a specific substance in cotton dust causing a daily fall in the ventilatory capacity of mill workers. Since then DR. R. S. F. SCHILLING and MR. S. A. ROACH, of the London School of Hygiene, had been responsible for the clinical and environmental studies; PROFESSOR W. D. M. PATON and MISS ANNE DAVENPORT, of the Department of Pharmacology, Royal College of Surgeons, had made pharmacological investigations; and DR. GILSON, MRS. MCDERMOTT, and the speaker, had been concerned with physiological studies. It had been found that the ventilatory capacity of 15 subjects (12 of them medical students of the Welsh National School of Medicine), who had never been exposed to cotton-mill dust, fell during a three-hour stay in a card-room. This, together with the slow onset of tightness in the chest, suggested that the action of the specific substance in cotton dust was not a usual allergic response. Experiments, involving the use of a plastic tent to enable the particle size of the mill dust inhaled to be varied, showed that fine dust under 7 μ in diameter was the most significant in producing the fall in ventilatory capacity. This was at variance with clinical evidence suggesting that byssinosis is worse in mills producing the greater quantity of coarse dust. Pharmacological investigations indicated that there was a constrictor substance in cotton dust, which was water soluble and resistant to boiling, but not soluble in common organic solvents. The constrictor action was not due simply to acetylcholine, histamine, or 5-hydroxytryptamine. The substance did not act via autonomic ganglion cells, and its exact nature had not yet been identified.

In reply to PROFESSOR BYWATERS, DR. MCKERROW said it was not known whether the substance responsible arose from the cotton plant itself or was a contaminant. PROFESSOR

STUART-HARRIS asked whether the physiological changes were similar to those reported after exposure to dusts containing graphite. DR. MCKERROW said he had not studied ventilatory changes after graphite inhalation, but had found that the maximum breathing capacity in coal miners was not reduced after their working shift, which suggested that coal dust did not produce an effect similar to cotton dust.

DR. J. C. GILSON reported that he had been studying this problem in Africans working in sisal mills and cotton ginneries, where the seed is separated from the cotton fibre. The sisal plant was as dusty as many cotton mills, but the dust had no effect on the ventilatory capacity. In the dusty ginnery the effect was about the same as in the card-rooms in Lancashire. Dust associated with flax processing also seemed to have a similar effect.

In reply to DR. C. D. NEEDHAM, DR. MCKERROW said the change in ventilatory function was most marked on a Monday after the week-end rest, but it did occur to a lesser degree on other days of the week. DR. J. S. LOGAN said that a similar syndrome was caused by flax dust. It had been observed as long ago as 1832 by Thackrah, and still existed as a clinical and industrial problem in the flax and linen industry. PROFESSOR MELVILLE ARNOTT asked whether the lung compliance was altered during the dyspnoea induced by cotton dust, but DR. MCKERROW said he had not measured this.

DR. J. G. SCADDING inquired whether the delay in the onset of typical symptoms in cotton workers, although the normal subject showed functional changes on first exposure, was to be explained by the supposition that the typical syndrome developed only after irreversible changes had developed. DR. MCKERROW reported that there were not sufficient data to answer this with certainty. In reply to DR. KENNETH ROBSON he said that approximately two-thirds of cotton workers in a dusty mill showed a fall in maximum breathing capacity greater than 5 per cent. DR. CHARLES FLETCHER commented on the relatively small changes in maximum breathing capacity that had been associated with quite severe symptoms. The maximum breathing capacity of some subjects had not been reduced outside the range generally considered normal. It was important to appreciate that a normal maximum breathing capacity did not exclude the symptom of dyspnoea due to increased airway resistance.

4. DR. S. W. STANBURY and DR. G. A. LUMB (introduced) described their experiences in *The Treatment of Uraemic Renal Osteodystrophy*. Three skeletal complications of chronic uraemia—renal rickets, azotaemic osteomalacia, and azotaemic hyperparathyroidism—were shown to be amenable to therapy. The first two conditions responded specifically to large doses (1·25 to 7·5 mg. daily) of calciferol or dihydrotachysterol. Treatment was followed by rapid disappearance of pain and by radiographic healing of rachitic metaphyses and Looser's nodes; the radiographic changes of associated hyperparathyroidism healed simultaneously. In all treated patients there was conspicuous improvement in muscular function. The accompanying metabolic changes were the same as those associated with the healing of nutritional rickets by smaller doses of vitamin D. Vitamin D promoted the net absorption and bodily retention of calcium and phosphorus; it increased serum phosphate, calcium, and citrate; it increased the rate of skeletal turnover as measured by radiocalcium. Administration of alkalis had neither beneficial clinical nor detectable metabolic effects. No deleterious effects were observed to follow treatment, and it was possible to correct deformities by orthopaedic surgery. In azotaemic hyperparathyroidism the dominant osseous lesion was osteitis fibrosa; the serum calcium was often normal, the serum phosphate and citrate elevated; and the measured rate of skeletal calcium turnover enormously increased. Vitamin D was contra-indicated in this group, and subtotal parathyroidectomy (3·6 g. parathyroid tissue removed) had been successfully performed in one patient. This procedure had the same effect as removing a parathyroid adenoma and, after operation, it was possible to administer safely the large doses of vitamin D needed to heal the bones.

PROFESSOR D. V. HUBBLE inquired whether renal clearances supported the belief that a rising blood-urea level in one patient was associated with improved nutrition. He said that DR. FRASER in Toronto had shown that vitamin-D resistant rickets could be successfully treated with a high phosphorus intake. This he, too, had confirmed in one patient. Had DR. STANBURY used high phosphorus diets in his patients in whom there was no evidence of hyperparathyroidism, or high calcium diets in the other groups?

DR. R. NASSIM agreed that the correction of acidosis with sodium bicarbonate in these cases appeared to have no beneficial effect on the calcium balance. His experience was mainly with children under 13, and adequate healing of bone lesions appeared to be achieved with very much smaller doses of calciferol, one-half to one milligram being quite sufficient.

DR. M. D. MILNE asked whether ectopic calcification of the blood-vessels occurred with calciferol treatment in these cases. DR. PAUL FOURMAN pointed out that one of the difficulties in treating patients with hypoparathyroidism with vitamin D was that the urinary excretion of calcium increased before the plasma level became normal. He asked whether in renal osteodystrophy large doses of vitamin D raised the urinary excretion of calcium, as in other patients. DR. DONALD HUNTER said that the speaker was to be congratulated on having given a truly model communication. A glance at the history of this subject took us back to 1912, when a young physician in Derby sought to discover why certain older children with rickets died after anaesthesia for operations to straighten their limbs. Chronic nephritis was found to be the cause, and so *renal rickets* was established as an entity. It was a great pleasure to see this colleague in full health and vigour seated immediately in front of the speaker: he was of course DR. HUGH BARBER.

In reply, DR. STANBURY said that they had not studied the effects of administering large amounts of phosphate, although they were aware of its use by Fraser and Nassim in vitamin-D resistant rickets. They were convinced that a moderate increase in blood urea could be due to increased intake of protein with improved appetite, and not to renal damage. Although they had seen arterial calcification follow the administration of vitamin D, this had not occurred in 10 carefully supervised patients of their own. In reply to DR. NASSIM, he agreed that rachitic children may respond to a daily dose of 0·5 to 1 mg. vitamin D; but in adults with osteomalacia it was sometimes necessary to increase the dose to 6·25 mg. or 7·5 mg. daily when smaller doses had proved clinically and metabolically ineffective. The very low urinary calcium level either increased slightly or remained virtually unchanged during treatment with vitamin D.

5. DR. B. E. C. NORDIN (introduced by PROFESSOR E. J. WAYNE) spoke about *Calcium Deficiency in Osteoporosis*. He said that if osteoporosis were defined as a skeletal disease characterized by a reduction in the amount of bone present without any change in its quality, then theoretically it could be produced by either a reduction in bone formation or an increase in bone destruction. The usually accepted theory was that it was due to reduced bone formation arising from a defect in the protein component of the skeleton. In animals, however, osteoporosis could be produced by giving a low calcium diet. Diet histories had been obtained from 81 cases of osteoporosis, and compared with similar histories from 96 control subjects of similar age and sex. The patients with osteoporosis had all been taking a diet low in calcium, protein, and vitamin D. Furthermore, the mean urinary calcium excretion in the osteoporotic patients was higher than in the controls, and the relationship between dietary intake and urinary excretion of calcium was therefore different in the two groups. Ten of the patients with osteoporosis were found to have steatorrhoea. Oral calcium supplements appeared to have relieved the backache in about 75 per cent. of the patients who were treated in this way. Balance studies in 12 patients showed that calcium supplements produced a strongly positive calcium balance in eight of them, and studies with radiocalcium did not suggest any reduction in new bone formation in the seven patients who had been investigated by this technique. These findings were compatible with the belief that clinical osteoporosis of the idiopathic, post-menopausal, and senile types might be the result of a prolonged negative calcium balance, but much more work would have to be done to settle the issue.

DR. NASSIM said that there appeared to be a difference in the dietary habits of patients suffering with osteoporosis in Glasgow as compared with the South of England. His dieticians had not found that patients with porosis had had an inadequate calcium intake. He agreed that a low calcium intake with adequate vitamin D could produce lighter bones. This alone, however, did not explain the sex difference and a tendency to slightly increased urinary calcium excretion. Furthermore, treatment with vitamin D and calcium had been tried, before hormone therapy, without evidence of marked improvement. PROFESSOR J. W. CROFTON pointed out that the dieticians who took the histories would be biased if they knew to which group the patients belonged. PROFESSOR RUSSELL FRASER doubted the importance of histories in assessing the patient's diet over the previous 20 years, but felt that the response to calcium treatment was all-important. Osteoporosis could be produced in rats by a low calcium diet, as DR. HARRISON in his Department had confirmed. He himself had studied the calcium balance of post-menopausal osteoporotic patients, and when given a high calcium diet most showed an unusually high positive balance, which was continued over two to three years. Osteoporosis, however, probably had multiple causes. PROFESSOR BYWATERS pointed out that the only criteria of the results of treatment were subjective, and he wondered whether this was satisfactory in the absence of placebo controls.

6. PROFESSOR H. N. ROBSON discussed some features of *Kuru—A New Disease*, which occurred with a frequency of about 10 per cent. among a primitive tribe, the Fore people, inhabiting a remote and isolated area in the mountains of Eastern New Guinea. The clinical features, which suggested diffuse cerebellar damage, were mainly those of generalized and ultimately very gross cerebellar damage. Death usually occurred nine to 12 months after the onset. Pathological examination of five cases was briefly described. To explore a possible genetic basis for the condition, a genealogical survey was made in part of the Fore area, and pedigrees which included 2,099 persons showed that, of 913 who had died, Kuru was given as the cause of death in 204 (177 female and 27 male subjects). In addition, a number of pedigrees had been obtained from observed cases of Kuru; analysis of this material suggested that Kuru might be controlled by a single autosomal gene, dominant to its allelomorph in female and recessive in male subjects. This tentative hypothesis was put forward only in view of the negative results so far obtained in studying environmental factors.

PROFESSOR A. V. NEALE asked whether the urine in Kuru disease contained any abnormal or unusual amounts of amino acids, and whether any of the numerous 'bush teas' drunk by Papuans contributed to the neurological symptoms. PROFESSOR ROBSON replied that the total excretion of amino acids was high, but no qualitative abnormality had been detected. No toxic agent likely to cause the condition had been identified.

After lunch, kindly provided by the Board of Governors of the United Cardiff Hospitals, the afternoon was devoted to a large number of excellent scientific demonstrations at the Royal Infirmary and at the Medical Research Council Pneumoconiosis Research Unit in Llandough Hospital.

Annual Dinner

The Annual Dinner was held in the City Hall, the Cardiff members kindly providing sherry beforehand. The President, Professor Harold Scarborough, was in the Chair. The Royal Toast coupled with the Prince of Wales was proposed by the President, who also spoke of the Association and welcomed the guests. The Vice-Chancellor of the University, Principal Fulton, replied.

Saturday Morning, April 11

7. PROFESSOR C. V. HARRISON, DR. D. N. S. KERR, PROFESSOR R. MILNES WALKER (introduced), and DR. S. P. V. SHERLOCK described *Congenital Hepatic Fibrosis* in 12 children who had portal hypertension associated with characteristic histological changes in the liver, comprising strands of dense fibrous tissue containing numerous dilated small bile-ducts, intervening islands of well-preserved liver tissue, and a paucity of fine branches of the portal vein. The patients came under observation between the ages of one and 16 years with hepatomegaly or bleeding from oesophageal varices. Splenomegaly developed in all 12, and portal hypertension was demonstrated in 10. There was no evidence of gross liver-cell malfunction, except in one child who died of liver failure. Eight children underwent portacaval anastamosis, and all have remained well after a mean follow-up of three years. Standard liver function tests were usually normal except the plasma alkaline phosphatase level, which was raised in five cases. Trans-splenic portal venography showed non-filling of peripheral portal vein branches in some patients. The only reliable diagnostic test was liver biopsy. In three patients there were anomalies of the gall-bladder or major bile-ducts, and two children had congenital cystic kidneys. Two others developed septicaemia. In these patients, and in 16 others in the literature, there was a familial concentration, suggesting a genetic basis. The association with cystic disease of the kidneys suggested that this disease was a variant of congenital cystic liver.

In reply to PROFESSOR A. V. NEALE, DR. KERR confirmed the fact that no history could be obtained of maternal illness during pregnancy. In answer to PROFESSOR L. J. WITTS, he said the children had suffered no ill effects from the portacaval anastamosis, and were not given a special diet.

8. PROFESSOR M. L. ROSENHEIM, DR. A. G. SPENCER, and DR. W. R. CATTELL and DR. R. MOULTON (introduced) discussed *Divided Renal Clearance Studies in Hypertensive Patients With Predominantly Unilateral Renal Disease*, in which the urological procedures and renal surgery had been performed by MR. D. R. DAVIES and the radiological investigations by DR. J. C. HODSON. The patients were selected from a large group referred because of hypertension and apparent unilateral renal disease. On the basis of clinical evaluation, pyelography, and renal angiography, however, most were found to have bilateral renal disease. Of the remainder, 28, of whom 23 had severe hypertension, had had

divided renal clearance studies made. Twelve of this group had subsequently had a nephrectomy, and had been followed up for a year or more, and one had had a renal artery anastomosis.

DR. SPENCER described the technique of divided renal clearance studies, and emphasized that great care was necessary in their performance and interpretation, because the results could be influenced by the passage of ureteric catheters, by the anaesthesia, and by the administration of drugs that lowered the blood-pressure. He showed that, whereas in essential hypertension there was little or no difference in the function of the two kidneys, in the present series of hypertensive patients with renal disease there was always a significant difference in the clearance of para-aminohippurate (PAH) and inulin, in the concentration of these substances in the urine, and in the rate of excretion of sodium and water. There was such excellent correlation between the studies of renal function and the appearances on renal angiography that for most patients divided clearance studies were not now considered necessary, because as much information could be obtained from undivided clearances of PAH and inulin together with angiograms. In pyelonephritis with hypertension the clearance of PAH was greatly reduced, and the ratio of inulin to PAH clearance ranged from 0·3 to 0·5, which was much higher than in essential hypertension. In unilateral disease the rate of sodium excretion was always less, and the concentration usually less, on the affected side. This did not necessarily indicate primary renal artery stenosis, nor that nephrectomy would be followed by a cure of the hypertension. In normotensive subjects with unilateral renal disease, DR. SPENCER showed that the clearances of inulin and PAH on the unaffected side were both greater than the normal values for one kidney. The better kidney was considered to show maximum compensatory hypertrophy when inulin clearance on that side equalled 120 minus inulin clearance on the diseased side. Of 23 patients, 14 had less than complete compensation by the better kidney, and all had evidence of hypertensive vascular disease in the better kidney, as shown by low clearance of PAH and a high ratio of inulin to PAH clearance. In nine patients who had undergone nephrectomy, with relief of hypertension in six and no benefit in three, the inulin clearance was over 80 ml. per minute and the PAH clearance over 250 ml. per minute in the better kidney. In 10 patients, considered unsuitable for nephrectomy because all similar reported cases had failed to improve, the clearances of inulin and PAH were respectively less than 50 and 200 ml. per minute in the better kidney. Four patients with values intermediate between these two groups had been operated on, with one success.

DR. TURNER asked whether divided clearance studies gave more information than could be obtained by estimations of specific gravity and of chloride and urea content in samples obtained from each kidney, together with the appearance time of injected indigo-carmine. He also inquired as to the different types of renal disease which had been diagnosed by aortography, the indications for using this technique, and whether the injection was made through a catheter inserted up the femoral artery.

PROFESSOR SMART asked whether renal biopsies had been carried out in these patients. He described a patient with deficient blood-flow to one kidney as a result of a large atheromatous plaque. The finding of vascular changes in the kidney, with good function, but a relatively normal histological appearance on the 'bad' side, had given the clue to the underlying cause of the hypertension.

PROFESSOR CROFTON asked whether any of the patients had complete absence of urinary secretion on the diseased side. DR. NEEDHAM inquired whether the impaired function of the remaining kidney improved after nephrectomy.

In reply DR. SPENCER said that measurement of the specific gravity and concentration of urine collected from both ureters was simple, but of little practical value. It was not helpful in diagnosis since, whatever the nature of the renal lesion, the concentrations and rates of excretion of sodium, urea, and other solutes were usually less from the more affected kidney; it was of no value in assessing whether nephrectomy would relieve the hypertension, and it provided no measurement of the function of the better kidney. The answers to these three important questions were best given by a combination of renal angiography and undivided clearances of inulin and para-aminohippurate. The indications for renal angiography could not be covered in a brief reply, but in general were those given in the papers by DR. POUTASSE. Renal angiography should be performed by the percutaneous trans-femoral artery technique. Renal biopsy had not been done for fear of damaging the better kidney. Complete absence of urine secretion had not been encountered, but the rate of flow could be very low.

9. DR. K. JEFFERSON, DR. G. SLOMAN (introduced), and DR. A. LEATHAM described their experience of *Coronary Angiography in Live Dogs*. This technique when applied to

man might be of value in the differential diagnosis of pain in the chest, in studying the natural history of coronary artery disease, and in assessing the results of medical and surgical treatment. DR. LEATHAM then described the technique in dogs of injecting contrast medium, via a catheter with side holes and a blocked end introduced via a peripheral artery, into the base of the aorta about 2 cm. above the aortic valve. The results were recorded by cine-angiocardiography at 32 frames per second. To obtain good visualization the aortic sinuses had to be filled in diastole, and for this a Valsalva manœuvre to reduce left ventricular ejection and drug-induced bradycardia to prolong diastole were less successful than producing cardiac arrest with acetylcholine. Good coronary filling with contrast medium produced some myocardial ischaemia, judged from ST and T-wave changes in the electrocardiogram, but this was transient, with an average duration of 30 seconds. Sinus rhythm returned spontaneously five to 15 seconds after the acetylcholine, and an external electric stimulator was available as an additional safeguard. No important complications had been encountered in 119 experiments on 25 dogs. An automatic device actuated by the electrocardiogram had been designed for use in man, so that the contrast medium could be injected in early diastole, and possibly cardiac arrest induced by acetylcholine avoided.

DR. DEUCHAR suggested that there might be considerable risk of myocardial ischaemia when this procedure was used in patients with coronary artery disease, if the injection led to ST changes in healthy dogs. PROFESSOR A. C. DORNHORST said that carotid sinus pressure might give a diastolic pause of sufficient length for the procedure, and prove safer than acetylcholine-induced cardiac arrest.

DR. JOHN MARSHALL suggested that pressure on the eyeballs, which had been used extensively to study the effects of vagal inhibition on the electroencephalogram, might be a useful method of producing temporary cardiac arrest. He doubted, however, whether much information would be obtained from coronary arteriography, as the analogous procedure of cerebral arteriography in acute cerebral infarction had not provided a great deal of information. A completely occluded vessel was not often seen, and the interpretation of irregularities in the lumen was very difficult.

DR. JOHN GOODWIN asked whether the transient anoxia from the contrast medium might not induce ventricular fibrillation in patients with coronary artery disease. PROFESSOR MELVILLE ARNOTT stressed the need for a reliable method of assessing coronary artery disease, particularly if anticoagulant treatment of indefinite duration were to be widely adopted. He thought the technique described would be safe in man with the exception of acetylcholine-induced cardiac arrest, and he hoped that the timing device, triggered by the cardiac cycle, would allow satisfactory filling of the coronary arteries without the necessity of stopping the heart. How much contrast medium was injected?

In reply DR. LEATHAM pointed out that the anoxia would affect the whole myocardium, and this was less likely to cause ventricular fibrillation than anoxia confined to a small area. From this it followed that selective injection into one coronary artery must be avoided. The best contrast medium was 76 per cent. Urografin, and in man about 50 ml. were injected as quickly as possible at a pressure of 120 lb. per sq. inch.

10. DR. E. M. MCGIRR spoke on *Sporadic Goitre due to Defects in Hormone Synthesis*. This work was a sequel to that presented to the Association in 1953, when it was shown that in patients with sporadic goitrous cretinism there was a defect in the synthesis of thyroid hormone. Further investigations established that the hypothyroidism and goitres in most of these patients were due to a deficiency of dehalogenase, but that this was only one of several defects subsequently defined in goitrous cretinism. By the use of similar techniques adolescent or young adult patients who were found to have large goitres and who were usually euthyroid had been investigated. In 10 such patients enzyme defects had been defined which resulted in failure to utilize trapped iodine, or impaired the ability to couple two molecules of di-iodotyrosine to yield thyroxine, or caused the loss of iodotyrosines because of impaired dehalogenase activity. In addition there was evidence, in three sisters with very large goitres, that there was an abnormal thyroid protein to which thyroxine was very firmly bound.

PROFESSOR RUSSELL FRASER reported the same chromatographic findings in the digests of thyroid biopsy specimens from similar patients. Non-toxic goitres showing an avidity for radioiodine also seemed to have similar enzyme defects, and possibly most non-toxic goitres might show this in lesser degrees. PROFESSOR ROBERT PLATT pointed out that it was important to test the father of the girl, described by DR. MCGIRR, who had dehalogenase deficiency and whose mother had the same defect to a lesser degree. The defect

could be a gene of variable expression, or one which was fully expressed only in the homozygote.

DR. WILLIAM PHILLIPS asked whether the criteria for the diagnosis of adenocarcinoma in the patient showing the dehalogenase defect had been purely histological. If so, he thought the change might prove of great theoretical interest in its possible relation to that seen in the thyroid after long-continued antithyroid medication, and he wondered whether this was, in a sense, an 'antithyroid' effect of lifelong duration. In reply to PROFESSOR A. V. NEALE, DR. MCGIRR said that 0·5 mg. thyroxine thrice daily was required to correct the hypothyroidism.

11. DR. G. R. TUDHOPE (introduced by PROFESSOR G. M. WILSON) discussed *Anaemia in Hypothyroidism*. The incidence and nature of anaemia had been determined in 116 patients with untreated primary hypothyroidism. In 79 cases there was no anaemia. A mild normocytic anaemia, for which no cause was apparent other than hypothyroidism, was present in five cases; in these cases the haemoglobin increased to normal during treatment with thyroxine alone. In hypothyroid patients without anaemia the volumes of red cells and of plasma were reduced in the same proportion; in the patients with mild normocytic anaemia the plasma volume was diminished relatively less than the red-cell volume. Microcytic anaemia, present in 17 cases, appeared to result from coincidental iron deficiency. No improvement in the blood resulted from thyroxine treatment, but the anaemia responded satisfactorily to iron. In some cases the adequate haematological response to iron was demonstrated before giving thyroxine, while the patient was still hypothyroid. Classical pernicious anaemia was present in 13 patients (11·2 per cent.). Apart from these patients, macrocytic anaemia was found in only two cases; it was probably associated with hepatic cirrhosis in one case, and with recent alimentary haemorrhage in the other. Because of this high incidence of pernicious anaemia, vitamin-B_{12} absorption was studied in 21 cases. Grossly impaired absorption, improved by the addition of intrinsic factor, was found in eight cases; seven of these had classical pernicious anaemia, and the eighth had vitamin-B_{12} deficiency resulting from failure of intrinsic factor activity, but had not yet developed blood or marrow changes. In 13 patients who had no haematological abnormality the absorption of vitamin B_{12} was within the normal range. This study showed that anaemia, apart from that due to deficiency of iron or vitamin B_{12}, was uncommon in hypothyroidism. There was an abnormally high incidence of pernicious anaemia in patients with hypothyroidism, but the reason for the association was not clear. The two conditions seemed to develop independently, and deficiency of thyroid hormone, by itself, did not lead to vitamin-B_{12} deficiency.

DR. BOMFORD said he had at one time been interested in a type of mild anaemia in hypothyroidism which responded slowly to thyroid alone. The red cells in his cases had shown no anisocytosis or poikilocytosis, but there was a small degree of macrocytosis, which disappeared as the red-cell count returned to normal. He did not think these were examples of pernicious anaemia. He wondered whether Dr. Tudhope's five cases reported as normocytic could, in fact, have been slightly macrocytic.

DR. A. G. MACGREGOR remarked that it was of interest that the incidence of pernicious anaemia in the group of patients with myxoedema secondary to previous treatment of hyperthyroidism was very little less than the incidence of pernicious anaemia in the group with idiopathic myxoedema. He asked whether DR. TUDHOPE had any knowledge of the incidence of pernicious anaemia in a large group of patients with untreated hyperthyroidism, and he also inquired about the nature of the treatment given for the thyrotoxicosis and the time interval that elapsed before the pernicious anaemia became apparent. PROFESSOR A. C. DORNHORST asked whether the cases of treated hyperthyroidism had all received radioiodine. PROFESSOR RUSSELL FRASER inquired about the time relationship between the onset of pernicious anaemia and the development of myxoedema in those patients who had received treatment for hyperthyroidism.

In reply DR. TUDHOPE said that in the five cases where the anaemia responded to thyroxine alone, the description of the red cells as normocytic was based on the appearance of blood films. Price-Jones's red-cell distribution curves had not been constructed, but in one case the mean corpuscular volume had been above the normal range, being 100 cu.μ. Pernicious anaemia was present in 12 out of 600 patients with thyrotoxicosis treated with radioiodine; most of these thyrotoxic patients were aged over 40 years. In each of the three cases in which hypothyroidism following treatment for thyrotoxicosis was associated with pernicious anaemia, the anaemia had been diagnosed several years before the development of hypothyroidism.

12. Dr. R. H. Girdwood and Dr. A. Doig (introduced) described *Some Defects of Absorption in Disease of the Small Intestine*, based on a study of 25 non-anaemic control patients, 25 control patients with pernicious anaemia, 26 patients with idiopathic steatorrhoea, three with adult coeliac disease, one with tropical sprue, three with extensive resection of the small intestine, two with reticuloses of the small intestine, two after total gastrectomy, 13 after partial gastrectomy, five after gastroenterostomy, four with jejunal diverticulosis, two with strictures and fistulae of the small intestine, and four with enterotransverse colostomies. The tests used, where applicable, were: estimations of faecal fat and nitrogen; measurement of the absorption of glucose and xylose; the augmented histamine test for gastric secretion; estimation of the serum vitamin-B_{12} level and of the absorption of folic acid; measurement of the absorption of ^{56}Co- or ^{58}Co-labelled cyanocobalamin, and the effects of intrinsic factor and antibiotics on the absorption of this vitamin. Since the clinical picture of small-intestine fistulae or diverticula could be similar to that of idiopathic steatorrhoea, precise diagnosis was important. In this series, malabsorption of vitamin B_{12} occurred in 40 per cent. of the cases of intestinal malabsorption of the sprue type, while there was malabsorption of folic acid in 83 per cent. Of the other patients, malabsorption of folic acid was found only in three who probably had extensive disease of the small intestine. After gastrectomy or gastroenterostomy, or where there were small-intestinal loops or fistulae, steatorrhoea occurred without malabsorption of folic acid. In addition to Addisonian pernicious anaemia, malabsorption of cyanocobalamin occurred as a result of removal of the intrinsic-factor-bearing area of the stomach by total gastrectomy, and from destruction, presumably by gastritis, of the remaining intrinsic-factor-bearing area after partial gastrectomy or gastroenterostomy. In these patients the absorption of vitamin B_{12} was improved by giving intrinsic factor. Malabsorption of cyanocobalamin also resulted from disease or resection of the ileum, and could not be corrected. Where B_{12} malabsorption was associated with blind or stagnant loops of small intestine, it could be improved with tetracycline or by surgery. Organisms (chiefly *E. coli*), obtained at operation from blind or stagnant loops, were able to absorb vitamin B_{12} from a culture medium. Under suitable conditions they could synthesize folic acid. Of the patients with idiopathic steatorrhoea or coeliac disease, 18 out of 23 had flat glucose-tolerance curves, while 11 out of 15 had malabsorption of xylose. Of these, two had normal absorption of glucose but not of xylose, and two had normal absorption of xylose but not of glucose. The various findings confirmed the view that folic acid was absorbed in the upper small intestine, and cyanocobalamin in the ileum.

Professor Russell Fraser asked why patients who had had a gastrectomy did not absorb fat, and Dr. Avery Jones wondered what had been the criteria for making a diagnosis of idiopathic steatorrhoea, and whether jejunal biopsies had been carried out. In reply Dr. Girdwood said the cause for malabsorption of fat after gastrectomy was not known, but appeared to be digestive impairment rather than an absorption defect. Jejunal biopsies had not been made. In three patients with idiopathic steatorrhoea there was a previous history of coeliac disease, and in five others there had been improvement of symptoms with a gluten-free diet. In every case there was malabsorption of two or more substances, and where indicated tests of pancreatic function had been done.

13. Dr. I. Porter, Dr. J. T. Scott, Dr. M. Lewis, and Dr. A. St. J. Dixon (introduced by Professor E. G. L. Bywaters) discussed *The Relationship of Gastrointestinal Bleeding to Oral Corticosteroids and Aspirin*. Whereas the incidence of peptic ulceration was apparently small in patients with rheumatic diseases treated with aspirin, 14 out of 63 treated with corticosteroids for two to eight years had developed proven peptic ulcers. It was found, however, that 12 of these 14 patients had in addition been taking salicylate preparations, usually aspirin, and it was now widely recognized that aspirin was a gastric irritant. To investigate the incidence and quantity of occult bleeding after various antirheumatic drugs, the radioactivity of the stools was measured in 32 patients who were suffering from rheumatoid arthritis or other rheumatic diseases, and whose circulating red cells had been labelled with ^{51}Cr. In 21 trials occult bleeding (defined as more than 2 ml. blood daily) was induced by aspirin in 14; in only four trials was there no significant bleeding, while three patients bled irrespective of treatment. Similar results were obtained with 'disprin', 'enseal' aspirin, and tabs. codeinae co. Bleeding had not been induced with sodium salicylate nor with corticosteroids, phenylbutazone, or chloroquin. The amount of bleeding induced by aspirin was usually less than 5 ml. daily, but this could cause anaemia in menstruating women, children, and patients having a poor diet. Some patients were unduly sensitive and bled excessively. In these sensitive subjects sodium salicylate was preferred and, in general, regular blood counts and occasional iron therapy were indicated. Dr. Dixon suggested that when given together aspirin might cause local irritation and corticosteroids increase the tendency to ulcer formation.

PROFESSOR HUBBLE asked to what extent aspirin treatment was responsible for the iron-deficiency anaemia that occurred in rheumatoid arthritis. PROFESSOR A. V. NEALE suggested that the anaemia arising during aspirin treatment might be aggravated by the precipitation in the intestine of iron as the very insoluble, and presumably non-absorbable, ferric salicylate. DR. SHERLOCK asked whether the sodium salicylate was absorbed, or whether the 'enseals' appeared undigested in the faeces. PROFESSOR PLATT inquired whether sodium salicylate not contained in enteric-coated capsules also failed to induce bleeding. DR. G. WATKINSON asked whether any studies of aspirin-induced bleeding had been made in normal subjects. The findings in patients with rheumatoid arthritis were extremely important, but there was evidence that gastric function was not normal in these patients. The big problem was to assess the risks in normal people taking aspirin.

DR. G. D. KERSLEY said that in a study of 60 patients with rheumatoid arthritis receiving moderate doses of aspirin, selected at random, 10 had large quantities of occult blood in the stools, and six stopped bleeding within a week of changing temporarily to pethidine. He had had two cases of severe recurrent haematemesis due to aspirin. Forty-five out of 178 patients had dyspepsia on aspirin, but 37 of these were comfortable on 'paynocil' (aspirin and glycerine) or 'disprin'. He would like to know the experience of others with 'panadol', which contained no aspirin. Coal-tar derivatives were invaluable in the treatment of rheumatoid arthritis, and could not be easily abandoned, although their risks must be realized.

DR. KERR asked whether dissolving aspirin or 'disprin' in a large volume of water reduced the likelihood of bleeding. DR. AVERY JONES asked how the radioactive technique for measuring occult blood compared with the ordinary benzidine test, and whether it excluded sampling errors. DR. F. D. HART asked whether prothrombin estimations had been carried out and, if so, whether any abnormal results had been obtained.

In reply, DR. DIXON said he had no direct information on the extent to which aspirin was responsible for the anaemia commonly found in rheumatoid arthritis, but he thought it might play an important role, especially where the anaemia was due to iron deficiency. Both enteric-coated and ordinary salicylate and aspirin tablets were absorbed, and satisfactory blood levels obtained. The coated tablets had not been excreted in the faeces. In two patients ordinary tablets of sodium salicylate had not caused bleeding. No study had yet been made with the present technique in normal subjects, but some of the patients reported had had osteoarthritis or 'fibrositis'. The bleeding was not confined to those with rheumatoid arthritis. The manner in which aspirin was taken made little difference to the incidence of bleeding. Most patients took calcium aspirin preparations dissolved in water. One patient who bled after aspirin also bled when the aspirin was crushed up in milk. A comparison between the radioactive technique and the ortho-toluidine method for detecting occult blood had been made in about 200 stool samples. There was a high proportion of false positives with the chemical method, but this was to be expected, as no precautions had been taken to exclude blood from the diet. For amounts of blood greater than 4 ml. daily, the number of false negatives by the chemical method was about 20 per cent., and this may have been due to sampling errors. Prothrombin times had not been done as a routine, but vitamin-K antagonism by salicylates was unlikely to alter the time unless the dose was sufficiently great to cause severe intoxication. Moreover, the bleeding was not related to salicylates in general, but only to aspirin.

14. DR. J. D. BLAINEY, DR. R. F. FLETCHER, DR. J. HARDWICKE, DR. J. F. SOOTHILL (introduced), and PROFESSOR J. R. SQUIRE discussed *The Value of Continuous Steroid Therapy in Adult Patients with the Nephrotic Syndrome*. During the period 1952–4 30 patients were treated conservatively with a high-protein diet. Since 1955 continuous steroid therapy had been used in almost all cases, with prophylactic penicillin, and effective hypotensive treatment when the diastolic blood-pressure exceeded 100 mm. Hg. During this period 37 patients had been studied. Mortality was substantially and significantly reduced in the steroid-treated series, although diverse conditions were included in both groups. A high proportion showed complete symptomatic recovery, and oedema, proteinuria, and anaemia generally disappeared or diminished. Biopsy findings showed that patients with minimal renal lesions responded rapidly, and those with proliferative changes more slowly, and that patients with membranous glomerulonephritis were apparently unresponsive. The need for long-continued treatment was underlined by transient relapses in about one-third of the patients, which could be controlled by increased steroid dosage. In contrast to the untreated series, these patients showed no increased impairment of renal function as a result of relapse.

PROFESSOR CLIFFORD WILSON said the correlation of results of steroid therapy in the

nephrotic syndrome with the histological changes in the kidney was of the greatest importance. It was becoming increasingly apparent that good long-term results were most often obtained in patients with minimal structural changes in the glomeruli as shown by renal biopsy. Clinically these patients showed little or no hypertension. Moreover, these were the features in patients who recovered spontaneously. Children more often followed this course, and also responded to steroids better than did adults. He thought the different distribution of cases with slight and severe glomerular damage in PROFESSOR SQUIRE'S treated and untreated groups might account for the differences in mortality. A reliable assessment of steroid therapy could be obtained only if treated and untreated groups were composed of patients with minimal glomerular damage.

DR. BERNARD SCHLESINGER said that in childhood nephrosis was a much more clearly defined syndrome, although the aetiology was still obscure. Like many other paediatricians, he had found that steroid therapy held out the greatest hope of bringing about a remission. The original method of giving a short course had proved disappointing, as, after dramatic improvement, a relapse usually occurred. Prolonged maintenance treatment was the most successful, the dose being dropped to a level capable of keeping the urine free of albumin, and being raised if albumin reappeared. How long was it necessary to continue steroid treatment, and was it possible to reduce the dose to zero without a relapse occurring? Had PROFESSOR SQUIRE found corticotrophin of value when cortisone had failed?

In reply, PROFESSOR SQUIRE reiterated that a favourable response to steroid treatment was not confined to patients with minimal renal damage proved histologically. The response of patients with proliferative changes, coupled with the improved mortality, was convincing evidence of the value of steroid therapy. He agreed that the range of conditions causing the nephrotic syndrome in children was smaller, and in them the even more favourable results from steroid therapy seemed proven. Continuous penicillin prophylaxis with long-continued steroid therapy was safer than the uncontrolled disease, and discontinuance of treatment remained a serious step. No advantage seemed to have been demonstrated with corticotrophin which could not be obtained with adequate cortisone dosage. The small incidence of serious side-effects from steroids in nephrotic patients might well be related to the high-protein, high-calcium diets given to these patients.

The Meeting ended with luncheon at the University Union, kindly provided by the Welsh National School of Medicine, and with excursions to a Welsh mining valley and the Vale of Glamorgan.

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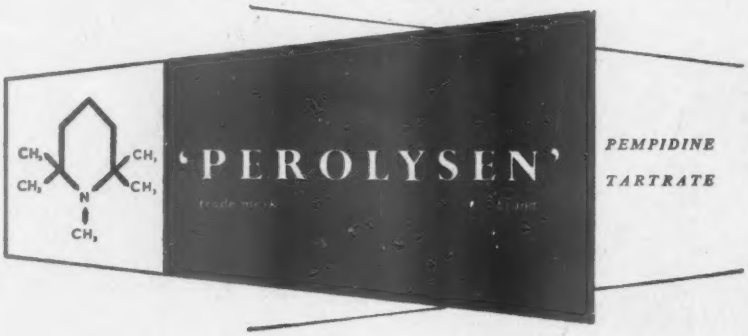

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